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FILE 'HOME' ENTERED AT 17:26:32 ON 29 JAN 2004

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FILE COVERS 1907 - 29 Jan 2004  VOL 140 ISS 5
FILE LAST UPDATED: 28 Jan 2004  (20040128/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s estrogen and amyloid
         65804 ESTROGEN
         46669 ESTROGENS
         77046 ESTROGEN
                 (ESTROGEN OR ESTROGENS)
         17307 AMYLOID
          1587 AMYLOIDS
         17389 AMYLOID
                 (AMYLOID OR AMYLOIDS)
L1         212 ESTROGEN AND AMYLOID

=> s 1 and estradiol
       7789321 1
         69513 ESTRADIOL
           347 ESTRADIOLS
         69599 ESTRADIOL
                 (ESTRADIOL OR ESTRADIOLS)
L2       30175 1 AND ESTRADIOL

=> s L1 and estradiol
         69513 ESTRADIOL
           347 ESTRADIOLS
         69599 ESTRADIOL
                 (ESTRADIOL OR ESTRADIOLS)
L3          86 L1 AND ESTRADIOL

=> s L3 and equine
          8400 EQUINE
           120 EQUINES
          8470 EQUINE
```

(EQUINE OR EQUINES)
L4 1 L3 AND EQUINE

=> d L4 ibib abs hitrn

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:973165 CAPLUS
TITLE: A comparison of the anti-inflammatory activities of conjugated **estrogens** and 17-.beta. **estradiol**
AUTHOR(S): Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.; Bryant, M.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, 33612-4799, USA
SOURCE: Inflammation Research (2003), 52(11), 452-460
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Unregulated chronic inflammatory process partly due to an **estrogen** deficiency may render postmenopausal women vulnerable to degenerative conditions such as arthritis, osteoporosis, atherosclerosis, and Alzheimer's disease. Current confusion regarding therapeutic efficacy of **estrogen** replacement therapy may be due to different **estrogen** formulations used, short term therapy, as well as advanced stage of the disease. We compared anti-inflammatory activities of two major **estrogen** prepns., conjugated **equine** **estrogen** (CEE) and 17-.beta. **estradiol**, using an animal model (rat mesentery) of in vivo inflammatory reaction to i.v. infused **amyloid**-.beta., examd. by video recording and subsequently analyzed by transmission electron microscopy. Cellular markers of inflammation were monitored: leukocyte migration, platelet activation, mast cell activation/degranulation, and endothelial disruption. Low doses of CEE (0.3 mg/kg for 3 wk) demonstrated significant anti-inflammatory activity, whereas even at high doses (2.0 mg) 17-.beta. **estradiol** had only minimal activity. CEE, a mixt. of several compds., may have some component(s) with significant anti-inflammatory activity. The anti-inflammatory activity of CEE may have a role in prevention of several degenerative diseases assocd. with menopause.

=> s L1 and equine
8400 EQUINE
120 EQUINES
8470 EQUINE
(EQUINE OR EQUINES)
L5 5 L1 AND EQUINE

=> d L5 1-5 ibib abs hitrn

L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:973165 CAPLUS
TITLE: A comparison of the anti-inflammatory activities of conjugated **estrogens** and 17-.beta. estradiol
AUTHOR(S): Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.; Bryant, M.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, 33612-4799, USA
SOURCE: Inflammation Research (2003), 52(11), 452-460
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal

LANGUAGE: English

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L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:575349 CAPLUS

DOCUMENT NUMBER: 139:317654

TITLE: An **estrogen** replacement therapy containing nine synthetic plant-based conjugated **estrogens** promotes neuronal survival

AUTHOR(S): Zhao, Lixia; Chen, Shuhua; Brinton, Roberta D.

CORPORATE SOURCE: Department of Molecular Pharmacology & Toxicology and Neuroscience Program, Pharmaceutical Sciences Center, University of Southern California, Los Angeles, CA, 90089, USA

SOURCE: Experimental Biology and Medicine (Maywood, NJ, United States) (2003), 228(7), 823-835
CODEN: EBMMBE; ISSN: 1535-3702

PUBLISHER: Society for Experimental Biology and Medicine

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Epidemiol. data from retrospective and case-control studies have indicated that **estrogen** replacement therapy can decrease the risk of developing Alzheimer's disease. In addn., **estrogen** replacement therapy has been found to promote neuronal survival both in vivo and in vitro. We have shown that conjugated **equine estrogens** (CEE), contg. 238 different mols. composed of **estrogens**, progestins, and androgens, exerted neurotrophic and neuroprotective effects in cultured neurons. In the current study, we sought to det. whether a steroidal formulation of nine synthetic conjugated **estrogens** (SCE) chem. derived from soybean and yam exts. is as effective as the complex multi-steroidal formulation of CEE. Analyses of the neuroprotective efficacy indicate that SCE exhibited significant neuroprotection against beta **amyloid**, hydrogen peroxide, and glutamate-induced toxicity in cultured hippocampal neurons. Indexes of neuroprotection included an increase in neuronal survival, a decrease in neurotoxin-induced lactate dehydrogenase release, and a redn. in neurotoxin-induced apoptotic cell death. Furthermore, SCE was found to attenuate excitotoxic glutamate-induced [Ca2+]i rise. Quant. analyses indicate that the neuroprotective efficacy of SCE was comparable to that of the multi-steroidal CEE formulation. Data derived from these investigations predict that SCE could exert neuroprotective effects comparable to CEE in vivo and therefore could reduce the risk of Alzheimer's disease in post-menopausal women.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:933950 CAPLUS
DOCUMENT NUMBER: 138:202924
TITLE: Animal model of **amyloid**-.beta. induced vascular inflammation and prevention by **estrogen** and other agents
AUTHOR(S): Rhodin, J.; Thomas, T.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, USA
SOURCE: World Congress for Microcirculation, submitted Papers, 7th, Sydney, Australia, Aug. 19-22, 2001 (2001), 543-547. Monduzzi Editore: Bologna, Italy.
CODEN: 69DILJ; ISBN: 88-323-1819-9
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Inflammatory processes play a prominent role in the pathol. of a no. of diseases ranging from arthritis, atherosclerosis, cancer and Alzheimer's disease. Utilizing a live animal (rat) model, and combining intravital video recordings of mesenteric microvascular bed with TEM analyses of the same vascular segments, the authors demonstrate inflammatory responses by arterioles and venules after infusion of **amyloid**-.beta.(1-40), the protein accumulating in brains of Alzheimer patients. The inflammatory responses were prevented by administering the following agents before the **amyloid**: (A) superoxide dismutase; (B) tumor necrosis factor-binding protein; (C) interleukin-1 receptor antagonist; (D) conjugated **equine estrogen**; (E) RAGE antibody.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:348873 CAPLUS
DOCUMENT NUMBER: 136:380367
TITLE: Effect of medroxyprogesterone acetate on vascular inflammatory markers in postmenopausal women receiving **estrogen**
AUTHOR(S): Wakatsuki, Akihiko; Okatani, Yuji; Ikenoue, Nobuo; Fukaya, Takao
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Kochi Medical School, Nankoku, Kochi, 783-8505, Japan
SOURCE: Circulation (2002), 105(12), 1436-1439
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Estrogen** increases C-reactive protein (CRP) in postmenopausal women. **Estrogen** also decreases cell adhesion mols., whereas elevated CRP stimulates the expression of cell adhesion mols. Because androgens have antiinflammatory effects, androgenic progestins such as medroxyprogesterone acetate (MPA) may inhibit proinflammatory effects of **estrogen**. We investigated the effects of MPA on **estrogen** -induced changes in acute inflammatory proteins and cell adhesion mols. in postmenopausal women. Postmenopausal women were treated daily with conjugated **equine estrogen** (CEE, 0.625 mg), CEE plus MPA 2.5 mg, or CEE plus MPA 5.0 mg for 3 mo. CEE significantly increased CRP concns. by 320.1.+-.210.2% ($P<0.05$). The addn. of MPA to CEE, however, inhibited the increase in CRP in a concn.-dependent manner (MPA 2.5 mg, 169.8.+-.66.9%, $P<0.05$; MPA 5 mg, 55.0.+-.30.4%, not significant). Similarly, CEE increased **amyloid** A protein concns., whereas MPA reversed this effect. Interleukin-6 concn. did not change significantly

in any treatment group. CEE alone significantly decreased the concn. of E-selectin, but the concns. of intercellular adhesion mol. and vascular cellular adhesion mol. did not change significantly. The addn. of MPA tended to decrease the levels of cell adhesion mols., and use of 5.0 mg MPA showed significant decreases in all cell-adhesion mol. concns. Concurrent MPA administration may attenuate **estrogen**'s proinflammatory effect. Because MPA in combination with CEE decreased cell adhesion mol. concns., the anti-inflammatory effect of MPA may actually be responsible for the favorable effect of **estrogen** -progestogen combinations on cell adhesion mols. in postmenopausal women.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:366985 CAPLUS

DOCUMENT NUMBER: 133:99758

TITLE: The **estrogen** replacement therapy of the Women's Health Initiative promotes the cellular mechanisms of memory and neuronal survival in neurons vulnerable to Alzheimer's disease

AUTHOR(S): Brinton, Roberta Diaz; Chen, Shuhua; Montoya, Marissa; Hsieh, Debra; Minaya, Jasmin

CORPORATE SOURCE: Department of Molecular Pharmacology and Toxicology and the Program in Neuroscience, Pharmaceutical Sciences Center, USC STAR Program, University of Southern California, Los Angeles, CA, 90033, USA

SOURCE: Maturitas (2000), 34(Suppl. 2), S35-S52
CODEN: MATUDK; ISSN: 0378-5122

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The current study investigated the neurotrophic and neuroprotective action of the complex formulation of conjugated **equine** **estrogens** (CEEs), the most frequently prescribed **estrogen** replacement therapy in the United States and the **estrogen** replacement therapy of the Women's Health Initiative. Videomicroscopic, morphol. and biochem. analyses were conducted in primary cultures of hippocampal neurons to det. the neurotrophic and neuroprotective properties of CEEs. Results of these analyses demonstrated that CEEs significantly increased hippocampal neuronal outgrowth, a cellular marker of memory formation. Dose response analyses indicated that the lowest effective concn. of CEEs exerted the maximal neurotrophic effect. Of neuroprotection studies demonstrated that CEES induced highly significant neuroprotection against beta amyloid25-35, hydrogen peroxide and glutamate-induced toxicity. CEEs induced cellular markers of memory function in neurons crit. to memory and vulnerable to neg. effects of aging and Alzheimer's disease. In addn., CEEs significantly and potently protected neurons against toxic insults assocd. with Alzheimer's disease. Because CEEs are the **estrogen** replacement therapy of the Women's Health Initiative, results of the current study could provide cellular mechanisms for effects of CEEs on cognitive function and risk of Alzheimer's disease derived from this prospective clin. trial.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s estrogen and amyloid beta
65804 ESTROGEN
46669 ESTROGENS
77046 ESTROGEN
(ESTROGEN OR ESTROGENS)
17307 AMYLOID

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          1587 AMYLOIDS
         17389 AMYLOID
                 (AMYLOID OR AMYLOIDS)
       1234929 BETA
          1326 BETAS
       1234995 BETA
                 (BETA OR BETAS)
          6387 AMYLOID BETA
                 (AMYLOID(W)BETA)
L6         105 ESTROGEN AND AMYLOID BETA

=> s L6 and equine
          8400 EQUINE
           120 EQUINES
          8470 EQUINE
                 (EQUINE OR EQUINES)
L7            3 L6 AND EQUINE

=> d L7 1-3 ibib abs hitrn

L7   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2003:973165  CAPLUS
TITLE:                   A comparison of the anti-inflammatory activities of
                         conjugated estrogens and 17-.beta. estradiol
AUTHOR(S):               Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.;
                         Bryant, M.
CORPORATE SOURCE:        Department of Anatomy, College of Medicine, University
                         of South Florida, Tampa, FL, 33612-4799, USA
SOURCE:                  Inflammation Research (2003), 52(11), 452-460
                         CODEN: INREFB; ISSN: 1023-3830
PUBLISHER:               Birkhaeuser Verlag
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Unregulated chronic inflammatory process partly due to an estrogen
     deficiency may render postmenopausal women vulnerable to degenerative
     conditions such as arthritis, osteoporosis, atherosclerosis, and
     Alzheimer's disease. Current confusion regarding therapeutic efficacy of
     estrogen replacement therapy may be due to different
     estrogen formulations used, short term therapy, as well as
     advanced stage of the disease. We compared anti-inflammatory activities
     of two major estrogen prepns., conjugated equine
     estrogen (CEE) and 17-.beta. estradiol, using an animal model (rat
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     subsequently analyzed by transmission electron microscopy. Cellular
     markers of inflammation were monitored: leukocyte migration, platelet
     activation, mast cell activation/degranulation, and endothelial
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     significant anti-inflammatory activity, whereas even at high doses (2.0
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     several compds., may have some component(s) with significant
     anti-inflammatory activity. The anti-inflammatory activity of CEE may
     have a role in prevention of several degenerative diseases assocd. with
     menopause.

L7   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2002:933950  CAPLUS
DOCUMENT NUMBER:         138:202924
TITLE:                   Animal model of amyloid-.beta.
                         induced vascular inflammation and prevention by
                         estrogen and other agents
AUTHOR(S):               Rhodin, J.; Thomas, T.
```

CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, USA
SOURCE: World Congress for Microcirculation, submitted Papers, 7th, Sydney, Australia, Aug. 19-22, 2001 (2001), 543-547. Monduzzi Editore: Bologna, Italy.
CODEN: 69DILJ; ISBN: 88-323-1819-9
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Inflammatory processes play a prominent role in the pathol. of a no. of diseases ranging from arthritis, atherosclerosis, cancer and Alzheimer's disease. Utilizing a live animal (rat) model, and combining intravital video recordings of mesenteric microvascular bed with TEM analyses of the same vascular segments, the authors demonstrate inflammatory responses by arterioles and venules after infusion of **amyloid-.beta**.(1-40), the protein accumulating in brains of Alzheimer patients. The inflammatory responses were prevented by administering the following agents before the amyloid: (A) superoxide dismutase; (B) tumor necrosis factor-binding protein; (C) interleukin-1 receptor antagonist; (D) conjugated **equine estrogen**; (E) RAGE antibody.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:366985 CAPLUS
DOCUMENT NUMBER: 133:99758
TITLE: The **estrogen** replacement therapy of the Women's Health Initiative promotes the cellular mechanisms of memory and neuronal survival in neurons vulnerable to Alzheimer's disease
AUTHOR(S): Brinton, Roberta Diaz; Chen, Shuhua; Montoya, Marissa; Hsieh, Debra; Minaya, Jasmin
CORPORATE SOURCE: Department of Molecular Pharmacology and Toxicology and the Program in Neuroscience, Pharmaceutical Sciences Center, USC STAR Program, University of Southern California, Los Angeles, CA, 90033, USA
SOURCE: Maturitas (2000), 34(Suppl. 2), S35-S52
CODEN: MATUDK; ISSN: 0378-5122
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The current study investigated the neurotrophic and neuroprotective action of the complex formulation of conjugated **equine estrogens** (CEEs), the most frequently prescribed **estrogen** replacement therapy in the United States and the **estrogen** replacement therapy of the Women's Health Initiative. Videomicroscopic, morphol. and biochem. analyses were conducted in primary cultures of hippocampal neurons to det. the neurotrophic and neuroprotective properties of CEEs. Results of these analyses demonstrated that CEEs significantly increased hippocampal neuronal outgrowth, a cellular marker of memory formation. Dose response analyses indicated that the lowest effective concn. of CEEs exerted the maximal neurotrophic effect. Of neuroprotection studies demonstrated that CEES induced highly significant neuroprotection against beta amyloid25-35, hydrogen peroxide and glutamate-induced toxicity. CEEs induced cellular markers of memory function in neurons crit. to memory and vulnerable to neg. effects of aging and Alzheimer's disease. In addn., CEEs significantly and potently protected neurons against toxic insults assocd. with Alzheimer's disease. Because CEEs are the **estrogen** replacement therapy of the Women's Health Initiative, results of the current study could provide cellular mechanisms for effects of CEEs on cognitive function and risk of Alzheimer's disease derived from this prospective clin. trial.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d L1 1-212 ibib abs hitrn

L1 ANSWER 1 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:68640 CAPLUS
TITLE: Hormone therapy and Alzheimer's disease: benefit or harm?
AUTHOR(S): Henderson, Victor W.
CORPORATE SOURCE: 4301 W Markham Street, Donald W Reynolds Center on Aging, University of Arkansas for Medical Sciences, 810, Little Rock, AR, 72205 USA, USA
SOURCE: Expert Opinion on Pharmacotherapy (2004), 5(2), 389-406
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease (AD) is the most common cause of dementia. After menopause, circulating levels of **estrogens** decline markedly and **estrogen** influences several brain processes predicted to modify AD risk. For example, **estrogen** reduces the formation of .beta.-**amyloid**, a biochem. hallmark of AD. **Estrogen** effects on oxidative stress and some effects on inflammation and the cerebral vasculature might also be expected to ameliorate risk. However, AD pathogenesis is incompletely understood and other **estrogen** actions could be deleterious. Limited clin. trial evidence suggests that **estrogen** therapy, begun after the onset of AD symptoms, is without substantial benefit or harm. Observational studies have assocd. **estrogen**-contg. hormone therapy with reduced AD risk. However, in the Women's Health Initiative Memory Study - a randomised, placebo-controlled trial of women 65 - 79 yr of age - oral **estrogen** plus progestin doubled the rate of dementia, with heightened risk appearing soon after treatment was initiated. Based on current evidence, hormone therapy is thus not indicated for the prevention of AD. Discrepancies between observational studies and the Women's Health Initiative clin. trial may reflect biases and unrecognised confounding factors in observational reports. Other explanations for divergent findings should be considered in future research, including effects of unopposed **estrogen** or different hormone therapy prepns. and the intriguing theor. possibility that effects of hormone therapy on AD risk may be modified by the timing of use (e.g., initiation during the menopausal transition or early postmenopause vs. initiation during the late postmenopause).

L1 ANSWER 2 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:20807 CAPLUS
TITLE: Use of peptides derived from junctional adhesion molecules to permeabilize mucosa for improved efficiency of mucosal delivery of therapeutic compounds
INVENTOR(S): Quay, Steven C.
PATENT ASSIGNEE(S): Nastech Pharmaceutical Company, Inc., USA
SOURCE: PCT Int. Appl., 426 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| WO 2004003145 | A2 | 20040108 | WO 2003-US19994 | 20030624 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-392512P P 20020628

AB Methods of improving the permeability of mucosal epithelia to improve the efficiency of transmucosal delivery of drugs are described. Permeability is improved by modulating epithelial junction structure or physiol. of the mucosa using a peptide derived from one of the proteins involved in the junction, such as junctional adhesion mols. (JAMs), occludins, or claudins. The permeabilizing agent is typically a peptide or peptide analog or mimetic, often selected or derived from an extracellular domain of a mammalian JAM, occludin or claudin protein. Identification of candidate peptides derived from junctional adhesion mol. JAM-1, claudins and occludins is demonstrated. The effects of the peptides were tested in a com. airway epithelium model. Tests in adult male volunteers showed a significant improvement in the delivery of human interferon .beta. across the nasal mucosa when a peptide derived from JAM-1 was included in an intranasal formulation.

IT INDEXING IN PROGRESS

L1 ANSWER 3 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:1002060 CAPLUS

TITLE: Impact of the selective **estrogen** receptor modulator, raloxifene, on neuronal survival and outgrowth following toxic insults associated with aging and Alzheimer's disease

AUTHOR(S): O'Neill, Kathleen; Chen, Shuhua; Brinton, Roberta Diaz

CORPORATE SOURCE: Pharmaceutical Sciences Center, Department of Molecular Pharmacology and Toxicology, University of Southern California, Los Angeles, CA, 90033, USA

SOURCE: Experimental Neurology (2004), 185(1), 63-80
CODEN: EXNEAC; ISSN: 0014-4886

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The current study investigated the **estrogen** agonist-antagonist properties of the selective **estrogen** receptor modulator, raloxifene (Ral), on neuroprotection and neuronal markers of memory function. Low concns. of raloxifene significantly reduced basal markers of membrane damage and had no deleterious effect on neuronal survival. However, high concns. of raloxifene (1000-5000 ng/mL) induced a significant increase in markers of membrane damage and a significant decrease in neuronal survival. At subtoxic concns., raloxifene induced significant neuroprotection against beta amyloid25-35-, hydrogen peroxide- and glutamate-induced toxicity. Results of analyses to det. whether raloxifene acted competitively or synergistically with 17 .beta.-estradiol revealed that a postmenopausal level of 17 .beta.-estradiol exerted a significantly greater increase in neuronal survival against beta-**amyloid**- and glutamate-induced toxicity compared to 50 ng/mL raloxifene. The combined presence of raloxifene and 17 .beta.-estradiol was significantly neuroprotective against beta amyloid25-35- and glutamate-induced excitotoxicity but was significantly lower than 17 .beta.-estradiol alone while not significantly different than raloxifene

alone. Morphol. analyses demonstrated that raloxifene significantly increased neuronal outgrowth of hippocampal neurons within a narrow dose range that was blocked by a glutamate NMDA receptor antagonist. Raloxifene did not promote the outgrowth of basal forebrain or cortical neurons. Results of this study indicate that raloxifene exerted partial **estrogen** agonist action in the absence of 17 .beta.-estradiol whereas in the presence of 17 .beta.-estradiol, raloxifene exerted a mixed **estrogen** agonist-antagonist effect.

L1 ANSWER 4 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:981428 CAPLUS
TITLE: The neuroprotective effects of **estrogen** in SK-N-SH neuroblastoma cell cultures
AUTHOR(S): Ba, Fang; Pang, Peter K. T.; Davidge, Sandra T.; Benishin, Christina G.
CORPORATE SOURCE: Faculty of Medicine, Department of Physiology, University of Alberta, Alta., Edmonton, T6G 2H7, Can.
SOURCE: Neurochemistry International (2004), 44(6), 401-411
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Estrogen** has been considered to be a neuroprotectant and a neuromodulator in many neuronal cell lines and tissue prepns. The protective effects of **estrogen** may be mediated through classical **estrogen** receptors (ERs), or may be due to its anti-oxidant properties which are independent of receptors. The current studies show that 17.beta.-estradiol (E2) is neuroprotective against .beta.-**amyloid** protein 25-35 (A.beta.)-, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-, high d. culture condition-, and serum deprivation-induced neuronal death in SK-N-SH human neuroblastoma cells. SK-N-SH cells express ER.beta., but not ER.alpha., as detected by Western blot anal. Among all the insults, MPTP, high d. culture and serum deprivation induce apoptotic cell death in this cell system as detected by ELISA detn. of mono/oligonucleosomes and DNA laddering, while A.beta. induces necrotic cell death. The protective effects of E2 are abolished by the addn. of tamoxifen and ICI 182,780 in the MPTP treated cells, but not in the other models, suggesting that the effect of E2 in the MPTP model is probably assocd. with activation of ER.beta.. The addn. of ICI 182,780 shows a mitogenic effect in SK-N-SH cells in the presence of E2 in control culture or in the A.beta. treated groups. Also, ICI 182,780 induced expression of ER.alpha.. Collectively, the current studies suggest that E2 is neuroprotective in apoptotic and necrotic death induced by multiple insults in SK-N-SH human neuroblastoma cells. Involvement of ER is insult type dependent. ICI 182,780 is able to influence the expression of ERs, probably through upregulation of ER.alpha. when ER.beta. is totally antagonized.

L1 ANSWER 5 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:973165 CAPLUS
TITLE: A comparison of the anti-inflammatory activities of conjugated **estrogens** and 17-.beta. estradiol
AUTHOR(S): Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.; Bryant, M.

TITLE: Oxidative nerve cell death in Alzheimer's disease and stroke: antioxidants as neuroprotective compounds
AUTHOR(S): Behl, Christian; Moosmann, Bernd
CORPORATE SOURCE: Max-Planck-Institute of Psychiatry, Munich, D-80804, Germany
SOURCE: Biological Chemistry (2002), 383(3/4), 521-536
CODEN: BICHF3; ISSN: 1431-6730
PUBLISHER: Walter de Gruyter GmbH & Co. KG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Many neurodegenerative disorders and syndromes are assocd. with an excessive generation of reactive oxygen species (ROS) and oxidative stress. The pathways to nerve cell death induced by diverse potential neurotoxins such as peptides, excitatory amino acids, cytokines or synthetic drugs commonly share oxidative downstream processes, which can cause either an acute oxidative destruction or activate secondary events leading to apoptosis. The pathophysiol. role of ROS has been intensively studied in in vitro and in vivo models of chronic neurodegenerative diseases such as Alzheimer's disease (AD) and of syndromes assocd. with rapid nerve cell loss as occurring in stroke. In AD, oxidative neuronal cell dysfunction and cell death caused by protofibrils and aggregates of the AD-assocd. **amyloid** .beta. protein (A.beta.) may causally contribute to pathogenesis and progression. ROS and reactive nitrogen species also take part in the complex cascade of events and the detrimental effects occurring during ischemia and reperfusion in stroke. Direct antioxidants such as chain-breaking free radical scavengers can prevent oxidative nerve cell death. Although there is ample exptl. evidence demonstrating neuroprotective activities of direct antioxidants in vitro, the clin. evidence for antioxidant compds. to act as protective drugs is relatively scarce. Here, the neuroprotective potential of antioxidant phenolic structures including .alpha.-tocopherol (vitamin E) and 17.beta.-estradiol (**estrogen**) in vitro is summarized. In addn., the antioxidant and cytoprotective activities of lipophilic tyrosine- and tryptophan-contg. structures are discussed. Finally, an outlook is given on the neuroprotective potential of arom. amines and imines, which may comprise novel lead structures for antioxidant drug design.

REFERENCE COUNT: 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 68 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:435240 CAPLUS
DOCUMENT NUMBER: 137:319846
TITLE: The search for .alpha.-secretase and its potential as a therapeutic approach to Alzheimer's disease
AUTHOR(S): Hooper, N. M.; Turner, A. J.
CORPORATE SOURCE: Proteolysis Research Group, School of Biochemistry and Molecular Biology, University of Leeds, Leeds, LS2 9JT, UK
SOURCE: Current Medicinal Chemistry (2002), 9(11), 1107-1119
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. In the nonamyloidogenic processing pathway the Alzheimer's **amyloid** precursor protein (APP) is proteolytically cleaved by .alpha.-secretase. As this cleavage occurs at the Lys16-Leu17 bond within the **amyloid** .beta. domain, it prevents deposition of intact amyloidogenic peptide. In addn., the large ectodomain (sAPP.alpha.) released by the action of .alpha.-secretase has several neuroprotective properties. Studies with a range of hydroxamic acid-based compds., such

as batimastat, indicate that .alpha.-secretase is a Zn metalloproteinase, and members of the adamalysin family of proteins, TACE, ADAM10, and ADAM9, all fulfil some of the criteria required of .alpha.-secretase. APP is constitutively cleaved by .alpha.-secretase in most cell lines. However, on stimulation with muscarinic agonists or activators of protein kinase C, such as phorbol esters, the .alpha.-secretase cleavage of APP is up-regulated. The constitutive .alpha.-secretase activity is primarily at the cell surface, while the regulated activity is predominantly located within the Golgi. The beneficial action of cholinesterase inhibitors may in part be due to activation of muscarinic receptors, resulting in an up-regulation of .alpha.-secretase. Other agents can also increase the nonamyloidogenic cleavage of APP including **estrogen**, testosterone, various neurotransmitters and growth factors. As the .alpha.-secretase cleavage of APP both precludes the deposition of the **amyloid** .beta. peptide and releases the neuroprotective sAPP.alpha., pharmacol. up-regulation of .alpha.-secretase may provide alternative therapeutic approaches for Alzheimer's disease.

REFERENCE COUNT: 147 THERE ARE 147 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 69 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:431766 CAPLUS

DOCUMENT NUMBER: 138:53396

TITLE: Regulation of DNA replication fork genes by 17.beta.-estradiol

AUTHOR(S): Lobenhofer, Edward K.; Bennett, Lee; Cable, P. Louann; Li, Leping; Bushel, Pierre R.; Afshari, Cynthia A.

CORPORATE SOURCE: Gene Regulation Group, National Institute of Environmental Health Sciences, Research Triangle Park, NC, 27709, USA

SOURCE: Molecular Endocrinology (2002), 16(6), 1215-1229
CODEN: MOENEN; ISSN: 0888-8809

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The steroid hormone **estrogen** can stimulate mitogenesis in hormone-responsive breast cancer epithelial cells. This action is attributed to the transcriptional activity of the ER, a ligand-dependent transcription factor. However, the exact mol. mechanism underlying **estrogen**-induced proliferation has yet to be completely elucidated. Using custom cDNA microarrays contg. many genes implicated in cell cycle progression and DNA replication, we examd. the gene expression of a hormone-responsive breast cancer cell line (MCF-7) treated with a mitogenic dose of **estrogen** in the absence of confounding growth factors found in serum. Gene expression changes were monitored 1, 4, 12, 24, 36, and 48 h after **estrogen** stimulation so that RNA levels at crit. times throughout cell cycle progression could be monitored. Significant changes include the altered transcript levels of genes implicated in transcription, cellular signaling, and cell cycle checkpoints. At time points during which increased nos. of cells were progressing through S phase, a majority of the genes assocd. with the DNA replication fork were also found to be induced. The coexpression of DNA replication fork genes by **estrogen** without the support of serum growth factors indicates an important **estrogen** regulatory component of the mol. mechanism driving **estrogen**-induced mitogenesis.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 70 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:354892 CAPLUS

DOCUMENT NUMBER: 137:379465
TITLE: Cholinesterase inhibitors do more than inhibit cholinesterase
AUTHOR(S): Svensson, Anne-Lie; Giacobini, Ezio
CORPORATE SOURCE: Division of Molecular Neuropharmacology, Department of Clinical Neuroscience, Occupational Therapy and Elderly Care Research (NEUROTEC), Clinical Neuroscience, Occupational Therapy and Elderly Care Research (NEUROTEC), Karolinska Institutet, Huddinge University Hospital, Huddinge, Swed.
SOURCE: Cholinesterases and Cholinesterase Inhibitors (2000), 227-235. Editor(s): Giacobini, Ezio. Martin Dunitz Ltd.: London, UK.
CODEN: 69COZC; ISBN: 1-85317-910-8
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. Although the main action of cholinesterase inhibitors is to inhibit the degrdn. of acetylcholine, other targets may be of importance and contribute to the clin. efficacy seen in Alzheimer's patients treated with these compds. Cholinesterase inhibitors may affect .beta.-**amyloid** aggregation and toxicity and the release of **amyloid** precursor protein, increase the release of noncholinergic neurotransmitters, and modulate the action of **estrogens**.
REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 71 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:348873 CAPLUS
DOCUMENT NUMBER: 136:380367
TITLE: Effect of medroxyprogesterone acetate on vascular inflammatory markers in postmenopausal women receiving **estrogen**
AUTHOR(S): Wakatsuki, Akihiko; Okatani, Yuji; Ikenoue, Nobuo; Fukaya, Takao
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Kochi Medical School, Nankoku, Kochi, 783-8505, Japan
SOURCE: Circulation (2002), 105(12), 1436-1439
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Estrogen** increases C-reactive protein (CRP) in postmenopausal women. **Estrogen** also decreases cell adhesion mols., whereas elevated CRP stimulates the expression of cell adhesion mols. Because androgens have antiinflammatory effects, androgenic progestins such as medroxyprogesterone acetate (MPA) may inhibit proinflammatory effects of **estrogen**. We investigated the effects of MPA on **estrogen** -induced changes in acute inflammatory proteins and cell adhesion mols. in postmenopausal women. Postmenopausal women were treated daily with conjugated equine **estrogen** (CEE, 0.625 mg), CEE plus MPA 2.5 mg, or CEE plus MPA 5.0 mg for 3 mo. CEE significantly increased CRP concns. by 320.1.+-.210.2% ($P<0.05$). The addn. of MPA to CEE, however, inhibited the increase in CRP in a concn.-dependent manner (MPA 2.5 mg, 169.8.+-.66.9%, $P<0.05$; MPA 5 mg, 55.0.+-.30.4%, not significant). Similarly, CEE increased **amyloid** A protein concns., whereas MPA reversed this effect. Interleukin-6 concn. did not change significantly in any treatment group. CEE alone significantly decreased the concn. of E-selectin, but the concns. of intercellular adhesion mol. and vascular cellular adhesion mol. did not change significantly. The addn. of MPA tended to decrease the levels of cell adhesion mols., and use of 5.0 mg MPA showed significant decreases in all cell-adhesion mol. concns. Concurrent MPA administration may attenuate **estrogen**'s

proinflammatory effect. Because MPA in combination with CEE decreased cell adhesion mol. concns., the anti-inflammatory effect of MPA may actually be responsible for the favorable effect of **estrogen** -progestogen combinations on cell adhesion mols. in postmenopausal women.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 72 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:323720 CAPLUS
DOCUMENT NUMBER: 137:210255
TITLE: Alzheimer's disease: An overview of current and emerging therapeutic strategies
AUTHOR(S): Jacobsen, J. Steven
CORPORATE SOURCE: Neuroscience Discovery Research, Wyeth Research, Princeton, NJ, 08543-8000, USA
SOURCE: Current Topics in Medicinal Chemistry (Hilversum, Netherlands) (2002), 2(4), 343-352
CODEN: CTMCCL; ISSN: 1568-0266
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Alzheimer's Disease (AD) is a progressive neurodegenerative disease that is prevalent among the elderly. It is a heterogeneous disease involving a no. of genetic components, risk factors and other poorly defined elements that all impact on the accumulation of beta-**amyloid** peptide (A.beta.). Current understanding of pathol., biochem. and genetics strengthens the notion that A.beta. is potentially the common pathogenic agent in an apparent convergence of various mechanisms leading to the decline of cognitive function and neuronal loss. While many issues remain controversial, recent evidence attributing A.beta. accumulation to cognitive decline in humans, coupled to the demonstrated improvement of cognitive function following A.beta. immunization in pre-clin. models, strongly supports the "**amyloid** hypothesis" and a central role for A.beta. in the pathophysiol. and etiol. of AD. These and other observations endorse the notion that therapeutic strategies targeting the inhibition of A.beta. accumulation by the use of protease inhibitors, immunization or other strategies, may provide disease-altering interventions to the development and progression of AD. The only approved and marketed treatments currently available for AD are the acetylcholinesterase inhibitors, a palliative strategy aimed at the temporary improvement of cognitive function. The purpose of this overview is to provide a brief understanding of key events leading to the progression of AD and to highlight a few of the current and most promising therapeutic strategies that one day might be available for the treatment of AD.
REFERENCE COUNT: 110 THERE ARE 110 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 73 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:302219 CAPLUS
DOCUMENT NUMBER: 137:379871
TITLE: Effect of APP17-mer peptide on neurodegeneration of hippocampal neurons in ovariectomized rats
AUTHOR(S): Yang, Fang; Wang, Pengwen; Ji, Zhijuan; Zhao, Zhiwei; Wang, Dongna; Shen, Shuli
CORPORATE SOURCE: Beijing Research Laboratory for Brain Aging, Beijing Xuan Wu Hospital, Beijing, 100053, Peop. Rep. China
SOURCE: Jiepou Xuebao (2002), 33(1), 42-46
CODEN: CPHPA5; ISSN: 0529-1356
PUBLISHER: Zhongguo Jiepou Xuehui
DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The neurotherapeutical effects of APP17 (**amyloid** protein precursor 17) peptide on neurodegeneration of hippocampal neurons in ovariectomized rats were studied. APP17 mer was synthesized by solid phase method and purified by HPLC. Adult rats were bilaterally ovariectomized, and APP17-mer peptide was injected after 6 wk as a curative. 12 Wk later, water maze testing of behavior was conducted, then fixative reagent was injected into the rats. Tissue specimens for each group were removed from hippocampal CA1 area for electron microscopy examn.; the cryostat section were studied by immunohistochem. for ER.alpha. (**estrogen** receptor .alpha.), NGF (nerve growth factor) and BDNF (brain-derived growth factor). OVX group had low blood estradiol level and APP17-mer peptide injection did not change its level. Full-course swimming time was clearly longer on OVX group, and the no. of errors was higher. The results in the APP17 mer-treated group were similar in the shamed-operated control group. The hippocampal ultrastructure showed abnormal change in the OVX group, but in the APP17 treated group it revealed integrity. The expressions of NGF and BDNF were reduced and ER.alpha. increased in the OVX group, but they became normal in the APP17 mer-treated group. APP17 peptide could improve the neurodegeneration not similar to **estrogen** but similar to neurotrophin.

L1 ANSWER 74 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:283762 CAPLUS

DOCUMENT NUMBER: 137:15931

TITLE: **Estrogen** lowers Alzheimer .beta.-**amyloid** generation by stimulating trans-golgi network vesicle biogenesis

AUTHOR(S): Greenfield, Jeffrey P.; Leung, Lawrence W.; Cai, Dongming; Kaasik, Krista; Gross, Rachel S.; Rodriguez-Boulan, Enrique; Greengard, Paul; Xu, Huaxi

CORPORATE SOURCE: Fisher Center for Research on Alzheimer's Disease and Laboratory of Molecular and Cellular Neuroscience, The Rockefeller University, New York, NY, 10021, USA

SOURCE: Journal of Biological Chemistry (2002), 277(14), 12128-12136
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Estrogen** reduces the risk of Alzheimer's disease in post-menopausal women, .beta.-**amyloid** (A.beta.) burden in animal models of Alzheimer's disease, and secretion of A.beta. from neuronal cultures. The biol. basis for these effects remains unknown. Here, utilizing cell-free systems derived from both neuroblastoma cells and primary neurons, the authors demonstrate that 17.beta.-estradiol (17.beta.-E2) stimulates formation of vesicles contg. the .beta.-**amyloid** precursor protein (.beta.APP) from the trans-Golgi network (TGN). Accelerated .beta.APP trafficking precludes maximal A.beta. generation within the TGN. 17.beta.-E2 appears to modulate TGN phospholipid levels, particularly those of phosphatidylinositol, and to recruit sol. trafficking factors, such as Rab11, to the TGN. Together, these results suggest that **estrogen** may exert its anti-A.beta. effects by regulating .beta.APP trafficking within the late secretory pathway. These results suggest a novel mechanism through which 17.beta.-E2 may act in **estrogen**-responsive tissues and illustrate how altering the kinetics of the transport of a protein can influence its metabolic fate.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 75 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:274111 CAPLUS
DOCUMENT NUMBER: 136:274573
TITLE: Octylphenol (OP) alters the expression of members of the **amyloid** protein family in the hypothalamus of the snapping turtle, Chelydra serpentina serpentina
AUTHOR(S): Trudeau, Vance L.; Chiu, Suzanne; Kennedy, Sean W.; Brooks, Ronald J.
CORPORATE SOURCE: Department of Biology and Centre for Advanced Research in Environmental Genomics, University of Ottawa, Ottawa, ON, K1N 6N5, Can.
SOURCE: Environmental Health Perspectives (2002), 110(3), 269-275
CODEN: EVHPAZ; ISSN: 0091-6765
PUBLISHER: National Institute of Environmental Health Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The gonadal **estrogen** estradiol-17.beta. (E2) is important for developing and regulating hypothalamic function and many aspects of reprodn. in vertebrates. Pollutants such as octylphenol (OP) that mimic the actions of **estrogens** are therefore candidate endocrine-disrupting chems. We used a differential display strategy (RNA-arbitrarily primed polymerase chain reaction) to isolate partial cDNA sequences of neurotransmitter, developmental, and disease-related genes that may be regulated by OP or E2 in the snapping turtle (Chelydra serpentina serpentina) hypothalamus. Hatchling and year-old male snapping turtles were exposed to a 10 ng/mL nominal concn. of waterborne OP or E2 for 17 days. One transcript [421 base pairs (bp)] regulated by OP and E2 was 93% identical to human APLP-2. APLP-2 and the **amyloid** precursor protein (APP) regulate neuronal differentiation and are also implicated in the genesis of Alzheimer disease in humans. Northern blot anal. detd. that the turtle hypothalamus contains a single APLP-2 transcript of 3.75 kb in length. Exposure to OP upregulated hypothalamic APLP-2 mRNA levels 2-fold ($p < 0.05$) in month-old and yearling turtles. E2 did not affect APLP-2 mRNA levels in hatchlings but stimulated a 2-fold increase ($p < 0.05$) in APLP-2 mRNA levels in yearling males. The protein .beta.-**amyloid**, a selectively processed peptide derived from APP, is also involved in neuronal differentiation, and accumulation of this neurotoxic peptide causes neuronal degeneration in the brains of patients with Alzheimer disease. Therefore, we also sought to det. the effects of **estrogens** on the expression of .beta.-**amyloid** . Using homol. cloning based on known sequences, we isolated a cDNA fragment (474 bp) from turtle brain with 88% identity to human APP. Northern blot anal. detd. that a single 3.5-kb transcript was expressed in the turtle hypothalamus. Waterborne OP also increased the expression of hypothalamic APP after 35 days of exposure. Our results indicate that low levels of OP are bioactive and can alter the expression of APLP-2 and APP. Because members of the APP gene family are involved in neuronal development, we hypothesize that OP exposure may disrupt hypothalamic development in young turtles.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 76 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:127599 CAPLUS
DOCUMENT NUMBER: 137:76581
TITLE: Neurohormonal signalling pathways and the regulation of Alzheimer .beta.-**amyloid** metabolism
AUTHOR(S): Gandy, Sam; Petanceska, Suzana
CORPORATE SOURCE: Department of Psychiatry, The Nathan S. Kline

Institute for Psychiatric Research, New York University, Orangeburg, NY, 10962, USA
SOURCE: Novartis Foundation Symposium (2000), 230(Neuronal and Cognitive Effects of Oestrogens), 239-253
CODEN: NFSYF7; ISSN: 1528-2511
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Alzheimer's disease (AD) is characterized by the intracranial accumulation of the 4 kDa **amyloid** .beta. peptide (A.beta.), following proteolysis of a .apprx. 700 amino acid, integral membrane precursor, the **amyloid** .beta. precursor protein (APP). The best evidence causally linking APP to AD was provided by the discovery of mutations within the APP coding sequence that segregate with disease phenotypes in autosomal dominant forms of familial AD (FAD). Though FAD is rare (< 10% of all AD), the hallmark features - **amyloid** plaques, neurofibrillary tangles, synaptic and neuronal loss, neurotransmitter deficits, dementia - are indistinguishable when FAD is compared with typical, common, "non-familial", or sporadic AD (SAD). Studies of some clin. relevant mutant APP mols. from FAD families have yielded evidence that APP mutations can lead to enhanced generation or aggregability of A.beta., consistent with a pathogenic role in AD. Other genetic loci for FAD were discovered which are distinct from the immediate regulatory and coding regions of the APP gene, indicating that defects in mols. other than APP can also specify cerebral amyloidogenesis and FAD. To date, all APP and non-APP FAD mutations can be demonstrated to have the common feature of promoting amyloidogenesis of A.beta.. Epidemiol. studies indicate that postmenopausal women on **estrogen** hormone replacement therapy (HRT) have their relative risk of developing SAD diminished by about 1-third as compared with age-matched women not receiving HRT. Because of the key role of cerebral A.beta. accumulation in initiating AD pathol., it is most attractive that estradiol might modulate SAD risk or age-at-onset by inhibiting A.beta. accumulation. A possible mechanistic basis for such a scenario is reviewed here.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 77 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:109178 CAPLUS
DOCUMENT NUMBER: 136:259190
TITLE: The activating enzyme of NEDD8 inhibits steroid receptor function
AUTHOR(S): Fan, Meiyun; Long, Xinghua; Bailey, Jason A.; Reed, Chad A.; Osborne, Elizabeth; Gize, Edward A.; Kirk, Eric A.; Bigsby, Robert M.; Nephew, Kenneth P.
CORPORATE SOURCE: Medical Sciences, Indiana University School of Medicine, Bloomington, IN, 47405, USA
SOURCE: Molecular Endocrinology (2002), 16(2), 315-330
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Coregulator proteins, coactivators and corepressors, have a profound influence on steroid receptor activity and play a role in regulating receptor levels. To identify novel coregulators of nuclear receptors, we used the ligand-binding and hinge region of ER.alpha. as bait in a yeast two-hybrid screen of a cDNA library derived from rat uterine luminal epithelium. We report the cloning and characterization of a cDNA encoding a protein homologous to yeast and human ubiquitin-activating enzyme 3 (Uba3), the catalytic subunit of the activating enzyme of the ubiquitin-like NEDD8 (neural precursor cell-expressed developmentally down-regulated) conjugation pathway (known as neddylation). Sequence

anal. revealed that Uba3 contains multiple nuclear receptor (NR)-interacting motifs (NR boxes), which are known to mediate interactions between coregulatory proteins and ligand-activated NRs. Yeast two-hybrid and glutathione-S-transferase pull-down assays demonstrated that Uba3 directly interacts with ligand-occupied ER.alpha. and ER.beta.. Transient transfection of Uba3 in mammalian cells inhibited ER-mediated transactivation in a time-dependent fashion; Uba3 had no effect on the initial events of transcriptional activation by liganded ER, but it blocked the progressive increase in target gene expression during continuous stimulation. Uba3 also inhibited transactivation by AR and PR in mammalian cells but had no effect on a steroid receptor-independent transactivation pathway. An enzymically silent form of Uba3 did not inhibit ER-induced transcription, and a Uba3-binding fragment of **amyloid** precursor protein-binding protein, the other subunit of the NEDD8-activating enzyme, partially overcame Uba3-mediated inhibition, demonstrating that the neddylation activity of Uba3 is required for its inhibition of steroid receptor transactivation. Thus, Uba3 inhibits transcription induced by steroid hormone receptors through a novel mechanism that involves the neddylation pathway. Understanding the mechanisms controlling hormone responsiveness of target tissues, such as the uterus and mammary gland, may lead to novel insights of therapeutic intervention.

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 78 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:89162 CAPLUS
DOCUMENT NUMBER: 137:103778
TITLE: Tamoxifen protects clonal mouse hippocampal (HT-22) cells against neurotoxins-induced cell death
AUTHOR(S): Gursoy, Erdal; Cardounel, Arturo; Al-Khlaiwi, Thamir; Al-Drees, Abdulmajeed; Kalimi, Mohammed
CORPORATE SOURCE: Department of Physiology, Virginia Commonwealth University, Medical College of Virginia, Richmond, VA, 23298-0551, USA
SOURCE: Neurochemistry International (2002), 40(5), 405-412
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the present work using an established clonal mouse hippocampal (HT-22) cell line, we have examd. whether the **estrogen** antagonist tamoxifen antagonizes the obsd. neuroprotective effects of **estrogen** against glutamate and **amyloid** beta protein neurotoxicity. Results obtained suggest that like **estrogen**, tamoxifen protects HT-22 cells against both 5 mM glutamate and 2 .mu.M **amyloid** beta protein induced cell death in a concn. dependent manner. Optimum protection was obtained at 500 nM tamoxifen. Tamoxifen was found to offer more potent protection at this dose against **amyloid** beta protein induced neurotoxicity when compared with glutamate neurotoxicity. We were unable to detect either **estrogen** receptor (ER)-ER.alpha. or ER.beta. presence in HT-22 cells using western blot technique. However, **amyloid** beta protein treatment significantly increases total glucocorticoid receptors (GRs) as detd. by western blot technique, while prior treatment with **estrogen** or tamoxifen followed by **amyloid** beta protein resulted in the redn. of total GRs to the levels comparable to that obsd. for the control untreated cells. In addn., using confocal immunofluorescence microscopy technique, we obsd. that 20 h of treatment with 2 .mu.M **amyloid** beta protein resulted in enhanced nuclear localization of GRs in HT-22 cells as compared to control untreated cells or 500 nM tamoxifen alone treated cells. Interestingly, 500 nM tamoxifen treatments for 24 h,

followed by 20 h treatment with 2 .mu.M **amyloid** beta protein resulted in dramatic redn. in GRs nuclear localization. In conclusion, tamoxifen (i) protects HT-22 cells against **amyloid** beta protein neurotoxicity and (ii) neuroprotective effect is independent of ERs.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 79 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:32213 CAPLUS

DOCUMENT NUMBER: 136:214873

TITLE: Modulation of A.beta. peptides by **estrogen** in mouse models

AUTHOR(S): Zheng, H.; Xu, H.; Uljon, S. N.; Gross, R.; Hardy, K.; Gaynor, J.; Lafrancois, J.; Simpkins, J.; Refolo, L. M.; Petanceska, S.; Wang, R.; Duff, K.

CORPORATE SOURCE: Huffington Center on Aging, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

SOURCE: Journal of Neurochemistry (2002), 80(1), 191-196
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Blackwell Publishing Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Clin. studies have shown that **estrogen** deprivation through menopause is a risk factor in both the initiation and progression of Alzheimer's disease (AD) and that **estrogen** replacement therapy may be protective. One of the major pathol. features in the human AD brain is the senile plaque, a proteinaceous structure composed mainly of heterogeneous peptides collectively known as A-beta (A.beta.). In vitro studies have linked **estrogen** with A.beta. modulation, suggesting that one way that **estrogen** depletion at menopause may exacerbate the features of AD is through A.beta. accumulation. To test this, two studies were performed on transgenic models of amyloidosis. Firstly, transgenic mice without detectable **amyloid** aggregates were subjected to ovariectomy and estradiol supplementation, and A.beta. levels were assessed. Secondly, the effects of **estrogen** modulation were assessed in mice at an age when plaques would be forming initially. Overall, A.beta. levels were higher in **estrogen**-deprived mice than intact mice, and this effect could be reversed through the administration of estradiol. These data suggest that, in vivo, **estrogen** depletion leads to the accumulation of A.beta. in the CNS, which can be reversed through replacement of estradiol. These results provide evidence that post-menopausal **estrogen** depletion may be linked to an increased risk of AD through A.beta. modulation.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 80 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:923165 CAPLUS

DOCUMENT NUMBER: 136:384204

TITLE: Investigations of a CA repeat in the **estrogen** receptor .beta. gene in patients with Alzheimer's disease

AUTHOR(S): Forsell, Charlotte; Enmark, Eva; Axelman, Karin; Blomberg, Mari; Wahlund, Lars-Olof; Gustafsson, Jan-Ake; Lannfelt, Lars

CORPORATE SOURCE: Department of Geriatric Medicine, Karolinska Institutet, Stockholm, S-141 86, Swed.

SOURCE: European Journal of Human Genetics (2001), 9(10), 802-804
CODEN: EJHGEU; ISSN: 1018-4813

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several studies have shown that **estrogen** treatment after menopause decreases the risk for Alzheimer's disease (AD). It is also known that **estrogen** stimulates the outgrowth of nerve cells and that apolipoprotein E (Apo E) synthesis and **amyloid** precursor protein (APP) metab. are regulated by **estrogen**. Recently a new **estrogen** receptor was identified, **estrogen** receptor .beta. (ER.beta.), located at chromosome 14q22-24. Several genes close to this chromosomal region have been implicated in AD, but the results are conflicting. Our hypothesis was that variations in the ER.beta. gene could be the underlying cause to the pos. findings in these genes and we have therefore investigated a CA repeat in intron 5 of the ER.beta. gene. Three hundred and thirty-six AD cases and 110 healthy age-matched controls were included in this study. Fourteen different alleles were found with frequencies between 0.1 and 37%. There was no significant difference between AD cases and controls when all alleles were compared. However, allele 5 was seen in 13.6% of the controls but only in 8.0% of AD cases (P=0.014; odds ratio (OR)=0.55). No AD patient homozygous for this allele was seen but three controls were homozygous. In conclusion, our findings suggest the ER.beta. allele 5 to be a protective factor. However, this has to be confirmed in a larger population.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 81 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:830470 CAPLUS
DOCUMENT NUMBER: 136:112111
TITLE: Neuroprotective mechanisms as treatment strategy in Alzheimer's disease
AUTHOR(S): Nordberg, Agneta
CORPORATE SOURCE: Karolinska Institutet, Department NEUROTEC, Division of Molecular Neuropharmacology, Geriatric Clinic, Huddinge University Hospital, Stockholm, S-141 86, Swed.
SOURCE: Current Medicinal Chemistry: Central Nervous System Agents (2001), 1(3), 239-246
CODEN: CMCCCO; ISSN: 1568-0150
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Alzheimer's disease is the most common dementia disorder characterized by a progressive loss of cognitive function. The major neuropathol. hallmark for the disease is the presence of beta **amyloid** (Ass) in the brain. The research to date indicates there are multiple factors that can trigger the development of Alzheimer's disease. Therefore there are at present several tentative treatment strategies being tested exptl. and clin. Symptomatic treatment with cholinesterase inhibitors is typically used currently for treatment of Alzheimer's disease. New treatment strategies having neuroprotective effects aim to influence the course of the disease and preventing or reducing Ass accumulation in the brain. This review covers recent findings regarding the exptl. and clin. experience with Alzheimer's treatments utilizing growth factors, anti-inflammatory drugs, anti-oxidants, **estrogens**, cholinergic agonists and anti-**amyloid** substances.
REFERENCE COUNT: 121 THERE ARE 121 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 82 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:794745 CAPLUS

DOCUMENT NUMBER: 136:96250
TITLE: Testosterone attenuates .beta.-**amyloid** toxicity in cultured hippocampal neurons
AUTHOR(S): Pike, Christian J.
CORPORATE SOURCE: Andrus Gerontology Center, University of Southern California, Los Angeles, CA, 90089-0191, USA
SOURCE: Brain Research (2001), 919(1), 160-165
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Accumulating evidence suggests that testosterone has neurotrophic and perhaps neuroprotective actions. Thus, age-related depletion of testosterone may increase the brain's vulnerability to Alzheimer's disease and related disorders. To begin investigating this issue, cultured neurons were exposed to the Alzheimer-related insult .beta.-**amyloid** in the presence of testosterone. .beta.-**Amyloid** neurotoxicity was significantly reduced by testosterone via a rapid, **estrogen**-independent mechanism. These data may provide addnl. insight into the treatment of age-related neurodegenerative disorders.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 83 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:780674 CAPLUS
DOCUMENT NUMBER: 135:313625
TITLE: Method using an arginine uptake inhibitor for treating Alzheimer's disease
INVENTOR(S): Colton, Carol A.; Czapiga, Meggan; Vitek, Michael P.
PATENT ASSIGNEE(S): Duke University, USA; Georgetown University
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001078715 | A1 | 20011025 | WO 2001-US12496 | 20010416 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-197584P P 20000417
AB Methods are provided for treating Alzheimer's disease with arginine uptake inhibitors, as are pharmaceutical formulations useful for carrying out the methods.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 84 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:776247 CAPLUS
DOCUMENT NUMBER: 136:292348
TITLE: The molecular bases of Alzheimer's disease and other neurodegenerative disorders
AUTHOR(S): Maccioni, Ricardo B.; Munoz, Juan P.; Barbeito, Luis

CORPORATE SOURCE: Millennium Institute for Advanced Studies in Cell Biology and Biotechnology, Faculty of Sciences, University of Chile, Santiago, Chile
SOURCE: Archives of Medical Research (2001), 32(5), 367-381
CODEN: AEDEER; ISSN: 0188-4409
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Alzheimer's disease, the cause of one of the most common types of dementia, is a brain disorder affecting the elderly and is characterized by the formation of two main protein aggregates: senile plaques and neurofibrillary tangles, which are involved in the process leading to progressive neuronal degeneration and death. Neurodegeneration in Alzheimer's disease is a pathol. condition of cells rather than an accelerated way of aging. The senile plaques are generated by a deposition in the human brain of fibrils of the .beta.-**amyloid** peptide (A.beta.), a fragment derived from the proteolytic processing of the **amyloid** precursor protein (APP). Tau protein is the major component of paired helical filaments (PHFs), which form a compact filamentous network described as neurofibrillary tangles (NFTs). Expts. with hippocampal cells in culture have indicated a relationship between fibrillary **amyloid** and the cascade of mol. signals that trigger tau hyperphosphorylations. Two main protein kinases have been shown to be involved in anomalous tau phosphorylations: the cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3.beta.. Cdk5 plays a crit. role in brain development and is assocd. with neurogenesis as revealted by studies in brain cells in culture and neuroblastoma cells. Deregulation of this protein kinase as induced by extracellular **amyloid** loading results in tau hyperphosphorylations, thus triggering a sequence of mol. events that lead to neuronal degeneration. Inhibitors of Cdk5 and GSK3.beta. and antisense oligonucleotides exert protection against neuronal death. On the other hand, there is cumulative evidence from studies in cultured brain cells and on brains that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells, leading to biochem. and structural abnormalities and neurodegeneration as related to the pathogenesis of Alzheimer's disease. This review is focused on the main protein aggregates responsible for neuronal death in both sporadic and familial forms of Alzheimer's disease, as well as on the alterations in the normal signaling pathways of functional neurons directly involved in neurodegeneration. The anal. is extended to the action of neuroprotective factors including selective inhibitors of tau phosphorylating protein kinases, **estrogens**, and antioxidants among other mols. that apparently prevent neuronal degeneration.

REFERENCE COUNT: 151 THERE ARE 151 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 85 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:768796 CAPLUS
DOCUMENT NUMBER: 137:39
TITLE: Alzheimer disease therapeutics
AUTHOR(S): Irizarry, Michael C.; Hyman, Bradley T.
CORPORATE SOURCE: Alzheimer Disease Research Unit, Center for Aging Genetics and Neurodegeneration, Massachusetts General Hospital, Boston, MA, 02129, USA
SOURCE: Journal of Neuropathology and Experimental Neurology (2001), 60(10), 923-928
CODEN: JNENAD; ISSN: 0022-3069
PUBLISHER: American Association of Neuropathologists, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Alzheimer disease (AD) is characterized pathol. by cholinergic deficits, **amyloid** plaques, neurofibrillary tangles, gliosis, and neuronal and synaptic loss. The primary therapeutic approach that has arisen from the pathol. anal. of AD brain has been cholinergic augmentation by cholinesterase inhibitors, which modestly improve cognitive function. Research on the underlying pathophysiol. dysfunction have focussed on AD-specific processes such as **amyloid** precursor protein, tau, and cerebral apolipoprotein E metab., and more general neurodegenerative processes such as inflammation, oxidn., excitotoxicity, and apoptosis. Rational neuroprotective approaches have led to recent trials of **estrogen**, antioxidant and anti-inflammatory medications in AD, and to the development of anti-**amyloid** strategies for delaying progression or preventing development of AD.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 86 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:763235 CAPLUS
DOCUMENT NUMBER: 135:314399
TITLE: Detection of variations in the DNA methylation profile of genes in the determining the risk of disease
INVENTOR(S): Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PATENT ASSIGNEE(S): Epigenomics A.-G., Germany
SOURCE: PCT Int. Appl., 636 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 68
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001077373 | A2 | 20011018 | WO 2001-DE1486 | 20010406 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10019058 | A1 | 20011220 | DE 2000-10019058 | 20000406 |
| WO 2001077373 | A2 | 20011018 | WO 2001-XA1486 | 20010406 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG | | | | |
| WO 2001077373 | A2 | 20011018 | WO 2001-XB1486 | 20010406 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, | | | | |

CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| EP 1274865 | A2 | 20030115 | EP 2001-953936 | 20010406 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| EP 1278892 | A1 | 20030129 | EP 2001-940158 | 20010406 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003531589 | T2 | 20031028 | JP 2001-575634 | 20010406 |
| EP 1360319 | A2 | 20031112 | EP 2001-955278 | 20010406 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| US 2003162194 | A1 | 20030828 | US 2003-240452 | 20030414 |
| JP 2004008217 | A2 | 20040115 | JP 2003-160375 | 20030605 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DE 2000-10019058 | A | 20000406 |
| DE 2000-10019173 | A | 20000407 |
| DE 2000-10032529 | A | 20000630 |
| DE 2000-10043826 | A | 20000901 |
| WO 2001-DE1486 | W | 20010406 |
| WO 2001-EP3969 | W | 20010406 |
| WO 2001-EP4016 | W | 20010406 |
| EP 2002-90203 | A | 20020605 |

AB The invention relates to an oligonucleotide kit as probe for the detection of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for detg. the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for detg. the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or assocd. syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or sexual dysfunction. This abstr. record is one of several records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.

L1 ANSWER 87 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

| | |
|---|---|
| ACCESSION NUMBER: | 2001:714455 CAPLUS |
| DOCUMENT NUMBER: | 136:245668 |
| TITLE: | Elevated gonadotropin levels in patients with Alzheimer disease |
| AUTHOR(S): | Short, Rodney A.; Bowen, Richard L.; O'Brien, Peter C.; Graff-Radford, Neill R. |
| CORPORATE SOURCE: | Department of Neurology, Mayo Clinic, Jacksonville, FL, USA |
| SOURCE: | Mayo Clinic Proceedings (2001), 76(9), 906-909 CODEN: MACPAJ; ISSN: 0025-6196 |
| PUBLISHER: | Dowden Health Media, Inc. |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |

AB To det. whether gonadotropin levels are elevated in patients with Alzheimer disease (AD). We measured LH (LH) and FSH (FSH) levels from stored plasma samples from 284 patients seen at a tertiary care center. We also reviewed their medical charts to record age and **estrogen** use in the women. The primary aim of our study was to det. whether

gonadotropin levels were elevated in 134 patients with AD compared with levels from 45 patients with frontotemporal dementia (FTD) and 105 cognitively normal controls. Although overlap between LH and FSH levels was considerable, LH (P=.046) and FSH (P=.007) were significantly elevated in **estrogen**-free women with AD (LH: median, 26.3 IU/L; interquartile range, 14.9-34.6 IU/L; FSH: median, 62.0 IU/L; interquartile range, 45.9-78.5 IU/L) compared with normal controls (LH: median, 20.1 IU/L; interquartile range, 13.7-25.3 IU/L; FSH: median, 47.7 IU/L; interquartile range, 34.1-57.5 IU/L). Levels of LH were also significantly higher (P=.03) in **estrogen**-free women with AD compared with women with FTD (LH: median, 20.7 IU/L; interquartile range, 19.0-28.5 IU/L; FSH: median, 53.3 IU/L; interquartile range, 27.6-77.9 IU/L). When we controlled for age, no differences in LH and FSH were obsd. in men with AD compared with normal controls. Gonadotropin levels are elevated in some patients with AD, ie, women not taking **estrogen**. Elevated gonadotropin levels may have a role in the prodn. of **amyloid**-.beta. protein, which is related to formation of senile plaques. Therefore, elevated gonadotropin levels may be involved in the pathogenesis of AD.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 88 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:708597 CAPLUS
DOCUMENT NUMBER: 136:79949
TITLE: **Estrogen** (E2) and glucocorticoid (Gc) effects on microglia and A.beta. clearance in vitro and in vivo
AUTHOR(S): Harris-White, M. E.; Chu, T.; Miller, S. A.; Simmons, M.; Teter, B.; Nash, D.; Cole, G. M.; Frautschy, S. A.
CORPORATE SOURCE: Department of Medicine, UCLA, Los Angeles, CA, 90095-1769, USA
SOURCE: Neurochemistry International (2001), 39(5-6), 435-448 CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The accumulation of fibrillar aggregates of .beta.-**amyloid** (A.beta.) in alzheimer's disease (AD) brain is assocd. with chronic brain inflammation. Although activated microglia (.mu.glia) can potentially clear toxic **amyloid**, chronic activation may lead to excessive prodn. of neurotoxins. Recent epidemiol. and clin. data have raised questions about the use of anti-inflammatory steroids (glucocorticoids, Gcs) and **estrogens** for treatment or prevention of AD. Since very little is known about steroid effects on .mu.glial interactions with **amyloid**, we investigated the effects of the synthetic Gc dexamethasone (DXM) and 17.beta.-estradiol (E2) in vitro in a murine .mu.glial-like N9 cell line on toxin prodn. and intracellular A.beta. accumulation. To det. whether the steroid alterations of A.beta. uptake in vitro had relevance in vivo, we examd. the effects of these steroids on A.beta. accumulation and .mu.glial responses to A.beta. infused into rat brain. Our in vitro data demonstrate for the first time that Gc dose-dependently enhanced .mu.glial A.beta. accumulation and support previous work showing that E2 enhances A.beta. uptake. Despite both steroids enhancing uptake, degrdn. was impeded, particularly with Gcs. Distinct differences between the two steroids were obsd. in their effect on toxin prodn. and cell viability. Gc dose-dependently increased toxicity and potentiated A.beta. induction of nitric oxide, while E2 promoted cell viability and inhibited A.beta. induction of nitric oxide. The steroid enhancement of .mu.glial uptake and impedence of degrdn. obsd. in vitro were consistent with observations from in vivo studies. In the brains of A.beta.-infused rats, the .mu.glial staining in entorhinal

cortex layer 3, not assocd. with A.beta. deposits was increased in response to A.beta. infusion and this effect was blocked by feeding rats prednisolone. In contrast, E2 enhanced .mu.glial staining in A.beta.-infused rats. A.beta.-immunoreactive (ir) deposits were quant. smaller, appeared denser, and were assocd. with robust .mu.glial responses. Despite the fact that steroid produced a smaller more focal deposit, total extd. A.beta. in cortical homogenate was elevated. Together, the in vivo and in vitro data support a role for steroids in plaque compaction. Our data are also consistent with the hypothesis that although E2 is less potent than Gc in impeding A.beta. degrdn., long term exposure to both steroids could reduce A.beta. clearance and clin. utility. These data showing Gc potentiation of A.beta.-induced .mu.glial toxins may help explain the lack of epidemiol. correlation for AD. The failure of both steroids to accelerate A.beta. degrdn. may explain their lack of efficacy for treatment of AD.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 89 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:706484 CAPLUS

DOCUMENT NUMBER: 136:15290

TITLE: **Estrogens** and hormone replacement therapy: Is there a role in the preservation of cognitive function?

AUTHOR(S): Bieber, Eric J.; Cohen, David P.

CORPORATE SOURCE: Pritzker School of Medicine, University of Chicago, Chicago, IL, USA

SOURCE: International Journal of Fertility and Women's Medicine (2001), 46(4), 206-209
CODEN: IJWMFW

PUBLISHER: Medical Science Publishing International

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Alzheimer's disease affects as many as 40% of Americans over the age of 80 and, as such, is a major public health issue. Interestingly, there is a two- to threefold greater prevalence in women than in men. It has been estd. that the prevalence of Alzheimer's disease will quadruple over the next half century. There have been implications of an effect of **estrogen** on neurol. function for many years. As long as 50 yr ago a study published in the gerontol. literature suggested that the administration of i.m. **estrogen** in a nursing home population was assocd. with improvement in memory and a delay in progression of memory loss. Most recently there has been great interest in the effect of **estrogen** on both neurons and the CNS vasculature. A study evaluating verbal memory and abstr. reasoning in over 700 women without dementia demonstrated that women who had used **estrogen** for as little as 1 yr had significant improvements in baseline cognitive testing. The pathogenesis of Alzheimer's disease and neurodementia is better understood today but remains incompletely elucidated. It has been suggested that inflammation exists both within the neurovasculature and the stroma and that beta-**amyloid** creates an inflammatory reaction. In Alzheimer's patients there are abnormal deposits of proteins such as beta-**amyloid**, presenelin, and apolipoprotein E-4. **Estrogen** may act as a protectant against these inflammatory mediating proteins. While a recent trial demonstrated no impact of **estrogen** in patients diagnosed with mild to moderate Alzheimer's, other studies have suggested that **estrogen** use significantly delays disease onset. One study followed over 1,100 subjects who were free of disease at trial initiation over a period of 1 to 5 yr. Even short-term use of **estrogen** imparted protection, although longer-term **estrogen** use was assocd. with greater protection. Unfortunately, most women are unaware of

the potential beneficial effect of **estrogen** on cognitive function. Prospective studies are under way to try to delineate how **estrogen** impacts Alzheimer's disease.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 90 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:691313 CAPLUS
DOCUMENT NUMBER: 135:353002
TITLE: **Estrogen** attenuates cell death induced by carboxy-terminal fragment of **amyloid** precursor protein in PC12 through a receptor-dependent pathway
AUTHOR(S): Chae, Hee-Sun; Bach, Jae-Hyung; Lee, Myoung-Woo; Kim, Hye-Sun; Kim, Yong-Sik; Kim, Kyung Yong; Choo, Kwan Young; Choi, Se Hoon; Park, Cheol-Hyoung; Lee, Sang Hyung; Suh, Yoo-Hun; Kim, Sung Su; Lee, Won Bok
CORPORATE SOURCE: Department of Anatomy, College of Medicine, Chung-Ang University, Seoul, S. Korea
SOURCE: Journal of Neuroscience Research (2001), 65(5), 403-407
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, we investigated effects of **estrogen** on cell death induced by carboxy-terminal fragment of **amyloid** precursor protein (CT), a candidate causative substance in the pathogenesis of Alzheimer's disease. 17.beta.-Estradiol attenuated CT-induced cell death in PC12 cells, whereas 17.alpha.-estradiol, nonestrogenic stereoisomer, did not exert any significant protective effect on CT-induced cell death. These results suggest that protective effects of **estrogen** may be mediated by **estrogen** receptor (ER) in PC12 cells. To confirm the results, we detd. the effects of tamoxifen, an **estrogen** receptor antagonist. Tamoxifen blocked the protective effects of 17.beta.-estradiol, although it did not affect those of 17.alpha.-estradiol. Overall, it might be thought that the protective effect of estradiol on CT-induced cell death is achieved by hormonal properties mediated through the **estrogen** receptor rather than the structural properties as a reducing agent.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 91 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:648714 CAPLUS
DOCUMENT NUMBER: 136:67757
TITLE: Regulation of Alzheimer .beta.-**amyloid** precursor trafficking and metabolism
AUTHOR(S): Gandy, Samuel; Petanceska, Suzana
CORPORATE SOURCE: Department of Psychiatry, The Nathan S. Kline Institute for Psychiatric Research, New York University, Orangeburg, NY, 10962, USA
SOURCE: Advances in Experimental Medicine and Biology (2001), 487(Neuropathology and Genetics of Dementia), 85-100
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review discussing the mechanism wherein estradiol modulates the sporadic Alzheimer's disease (SAD) risk or age-at-onset by inhibiting A.beta. accumulation. Topics covered include assocn. of AD with intracranial amyloidosis; A.beta. as a catabolite of an integral precursor; pathogenic

**amyloid** precursor protein (APP) mutations and Alzheimer-like phenotypes in transgenic mouse models in vivo; APP regulation through signal transduction processing; insights into mechanisms of regulated APP processing; therapeutic manipulation of A.beta. generation via ligand or hormonal manipulations; and A.beta. levels regulation in exptl. animals with **estrogen**.

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 92 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:611172 CAPLUS
DOCUMENT NUMBER: 135:339494
TITLE: Apolipoprotein E isoform-specific disruption of phosphoinositide hydrolysis: protection by **estrogen** and glutathione
AUTHOR(S): Cedazo-Minguez, A.; Cowburn, R. F.
CORPORATE SOURCE: Division of Experimental Geriatrics, Karolinska Institutet, NEUROTEC, NOVUM, KFC, Huddinge, 141 86, Swed.
SOURCE: FEBS Letters (2001), 504(1,2), 45-49
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mechanism(s) by which the E4 isoform of apolipoprotein E (apoE4) influences Alzheimer's disease (AD) are not fully known. The authors report that apoE4, but not apoE3, disrupts carbachol-stimulated phosphoinositide (PI) hydrolysis in SH-SY5Y neuroblastoma cells. Carbachol responses were also disrupted by .beta.-**amyloid** (A.beta.) (1-42) and apoE4/A.beta.(1-42) complexes, but not by apoE3/A.beta.(1-42). Glutathione and **estrogen** protected against apoE4 and A.beta.(1-42) effects, as well as those of H2O2. **Estrogen** protection was partially blocked by wortmannin, suggesting the involvement of phosphatidylinositol 3-kinase. An apoE4-induced disruption of acetylcholine muscarinic receptor-mediated signaling may explain the lower effectiveness of cholinergic replacement treatments in apoE4 AD patients. Also, the beneficial effect of **estrogen** in AD may be partially due to its ability to protect against apoE4- and A.beta.(1-42)-mediated disruption of PI hydrolysis.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 93 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:599325 CAPLUS
DOCUMENT NUMBER: 135:252139
TITLE: **Estrogen** induces a rapid secretion of **amyloid** .beta. precursor protein via the mitogen-activated protein kinase pathway
AUTHOR(S): Manthey, Dieter; Heck, Stefanie; Engert, Stefanie; Behl, Christian
CORPORATE SOURCE: Independent Research Group Neurodegeneration, Max Planck Institute of Psychiatry, Munich, 80804, Germany
SOURCE: European Journal of Biochemistry (2001), 268(15), 4285-4291
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The female sex hormone **estrogen** (17.beta.-estradiol; E2) may function as a neurohormone and has multiple neuromodulatory functions in the brain. Its potent neuroprotective activities can be dependent and independent of **estrogen** receptors (ERs). In addn., E2

influences the processing of the **amyloid** .beta. precursor protein (APP), one central step in the pathogenesis of Alzheimer's disease. Here, the authors show that physiol. concns. of E2 very rapidly cause an increased release of secreted nonamyloidogenic APP (sAPP.alpha.) in mouse hippocampal HT22 and human neuroblastoma SK-N-MC cells and that this effect is mediated through E2 via the phosphorylation of extracellular-regulated kinase 1 and 2 (ERK1/2), prominent members of the mitogen-activated protein kinase (MAPK) pathway. Furthermore, the authors show that the activation of MAPK-signaling pathway and the enhancement of the sAPP release is independent of ERs and could be induced by E2 to a similar extent in neuronal cells either lacking or overexpressing a functional ER.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 94 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:597767 CAPLUS
DOCUMENT NUMBER: 135:175405
TITLE: Method of reducing aluminum levels in the central nervous system
INVENTOR(S): Croom, Warren J., Jr.; Berg, Brian M.; Taylor, Ian L.
PATENT ASSIGNEE(S): North Carolina State University, USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001058409 | A2 | 20010816 | WO 2001-US3952 | 20010207 |
| WO 2001058409 | A3 | 20020221 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2001036737 | A5 | 20010820 | AU 2001-36737 | 20010207 |

PRIORITY APPLN. INFO.: US 2000-499980 A2 20000208
WO 2001-US3952 W 20010207

OTHER SOURCE(S): MARPAT 135:175405

AB A method of reducing aluminum concns. in the central nervous system of a subject (e.g., a patient afflicted with Alzheimer's disease or at risk of developing Alzheimer's disease) comprises administering to subject a pancreatic polypeptide receptor (PYY receptor) agonist in an amt. effective to reduce aluminum concns., levels or amts. in the central nervous system of the subject. Compns. useful for carrying out the method are also disclosed.

L1 ANSWER 95 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:512008 CAPLUS
DOCUMENT NUMBER: 135:267450
TITLE: **Estrogen** protects neuronal cells from **amyloid** .beta.-induced apoptotic cell death
AUTHOR(S): Hosoda, Tetsuya; Nakajima, Hiroo; Honjo, Hideo
CORPORATE SOURCE: Departments of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Kyoto, 602-8566,

Japan
SOURCE: NeuroReport (2001), 12(9), 1965-1970
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Accumulating studies have shown that **estrogen** replacement therapy reduces the risk of Alzheimer's disease. In this study, the authors clarified that 17.beta.-estradiol (E2) significantly rescues PC12 neuronal cells from **amyloid** .beta. protein (A.beta.)-induced cell death. The authors found that the amino acid residues of 25 to 35 (A.beta.25-35) were more cytotoxic than the full length protein (A.beta.1-40) and these residues induced DNA fragmentation typical for apoptosis. In addn., E2 was confirmed to inhibit calcium influx and cytochrome c release induced by A.beta.25-35. Since these sequential events cause apoptosis, the protective effect of E2 may be exerted not by the direct interaction with A.beta., but by the blockade of the mitochondrial apoptotic pathway induced by A.beta..
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 96 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:512004 CAPLUS
DOCUMENT NUMBER: 135:267449
TITLE: **Estrogen** protects against .beta.-**amyloid**-induced neurotoxicity in rat hippocampal neurons by activation of Akt
AUTHOR(S): Zhang, Lei; Rubinow, David R.; Xaing, Gou-Qaing; Li, Bing-Sheng; Chang, Yoong H.; Maric, Dragan; Barker, Jeffery L.; Ma, Wu
CORPORATE SOURCE: Behavioral Endocrinology Branch NIMH, NIH, Bethesda, MD, 20892, USA
SOURCE: NeuroReport (2001), 12(9), 1919-1923
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cellular mechanisms underlying the neuroprotective effects of **estrogen** are only beginning to be elucidated. Here the authors examd. the role of protein kinase B (Akt) activation in 17.beta.-estradiol (E2) inhibition of .beta.-**amyloid** peptide (31-35) (A.beta.31-35)-induced neurotoxicity in cultured rat hippocampal neurons. A.beta.31-35 (25-30 .beta.M) significantly decreased the total no. of microtubule assocd. protein-2 pos. cells (MAP2+). This decrease was significantly reversed by pre-treatment with 100 nM E2. Further, 100 nM E2 alone significantly increased the total no. of protein kinase B and microtubule assocd. protein-2 pos. cells compared with controls. Such E2-induced increases were inhibited by LY294002 (20 .mu.M), a specific PI3-K inhibitor, as well as by tamoxifen, an **estrogen** receptor antagonist/selective **estrogen** receptor modulator. These results indicate that the neuroprotective effects of E2 may be mediated at least in part via **estrogen** receptor-mediated protein kinase B activation.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 97 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:480779 CAPLUS
DOCUMENT NUMBER: 135:29184
TITLE: Effect of HRT on Alzheimer's disease
AUTHOR(S): Honjo, Hideo; Iwasa, Koichi; Hosoda, Tetsuya
CORPORATE SOURCE: Dep. Obstet. Gynecol., Kyoto Prefect. Univ. Med.,

Japan
SOURCE: Horumon to Rinsho (2001), 49(5), 501-507
CODEN: HORIAE; ISSN: 0045-7167
PUBLISHER: Igaku no Sekaisha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 36 refs., on (1) clin. symptoms, diagnosis, and pathogenesis of Alzheimer's disease (AD), (2) effects of **estrogens** on the apoE-mediated **amyloid** .beta.-protein deposition, neurofibrillary tangle, proliferation and differentiation of neurons and glia cells, formation and metab. of neurotransmitters, and neuroprotection, (3) prevention of AD by **estrogen** replacement therapy, and (4) clin. efficacy of **estrogen** in the treatment of AD.

L1 ANSWER 98 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:467553 CAPLUS
DOCUMENT NUMBER: 135:225187
TITLE: Reduced cerebrospinal fluid estradiol levels are associated with increased .beta.-**amyloid** levels in female patients with Alzheimer's disease
AUTHOR(S): Schonknecht, P.; Pantel, J.; Klinga, K.; Jensen, M.; Hartmann, T.; Salbach, B.; Schroder, J.
CORPORATE SOURCE: Department of Psychiatry, Section of Geriatric Psychiatry, University of Heidelberg, Heidelberg, D-69115, Germany
SOURCE: Neuroscience Letters (2001), 307(2), 122-124
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent in-vitro studies indicate that **estrogens** such as 17.beta.-estradiol (E2) may decrease the prodn. of .beta.-**amyloid** 1-42 (A.beta.42), a peptide central for the formation of senile plaques in Alzheimer's disease (AD). To test this hypothesis in a clin. study, cerebrospinal fluid levels of E2 were compared between 30 female AD patients and 11 female patients with non-dementing diseases such as major depression and investigated with respect to .beta.-**amyloid** 1-40 and A.beta.42 levels. E2 levels were significantly ($P<0.05$) lower in the AD group than in controls; within the AD group E2 levels were inversely correlated with A.beta.42 concns. ($r=-0.36$, $P=0.05$). This is the first clin. study providing evidence for an influence of E2 on A.beta.42 metab. in vivo. This observation corresponds to the putative beneficial effects of **estrogen** replacement therapy on the development and course of AD.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 99 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:463849 CAPLUS
DOCUMENT NUMBER: 135:175700
TITLE: Alzheimer's disease and **estrogen**
AUTHOR(S): Honjo, Hideo; Kikuchi, Noriko; Hosoda, Tetsuya; Kariya, Keiko; Kinoshita, Yoshiyuki; Iwasa, Koichi; Ohkubo, Tomoharu; Tanaka, Kazunori; Tamura, Takaya; Urabe, Mamoru; Kawata, Mitsuhiro
CORPORATE SOURCE: Dep. Gynecol., Kyoto Prefectural Univ. Med., Kyoto, 602-8566, Japan
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (2001), 76(1-5), 227-230
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The preventive effect of **estrogen** on Alzheimer's disease (AD) has become clear with epidemiol. data. Therapeutic effects of **estrogen** have not yet been established. In this presentation, we report our new basic and clin. data. The **estrogen** receptor (ER).alpha., and ER.beta. mRNA were investigated in rat brain. Estradiol-17.beta. (E2) treatment following OVX reduced the levels of ER.alpha. mRNA in the hypothalamus. In the substantia innominate (SI), the no. of choline acetyltransferase immunoreactive cells increased significantly in the **estrogen** treatment rat. The neurons in SI projecting to the forebrain cortex contained ER.alpha.. Increasing amts. of intracellular calcium, peroxidn., and apoptosis with **amyloid** .beta. were suppressed in neuronal cells from rat pheochromocytoma (PC12) cells with E2, ER.alpha. cDNA transfected PC 12 cells elaborated more neurite-like processes with E2. In clinics, we are currently prepg. vaginal progesterone tablets, which essentially may conc. in the endometrium to prevent endometrial cancer, with few general circulation of progesterone inviting less depression. The therapeutic effects of cyclic **estrogen**, such as its preventive effect, are suggested in these studies, at least on mild AD.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 100 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:453343 CAPLUS

DOCUMENT NUMBER: 135:43090

TITLE: Microwave unit and system for tissue processing

INVENTOR(S): Essenfeld, Ervin; Essenfeld, Harold; Morales, Azorides; Kimrey, Harold; Shahin, Ali

PATENT ASSIGNEE(S): University of Miami, USA

SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001044784 | A1 | 20010621 | WO 2000-US33761 | 20001214 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-170545P P 19991214

AB An improved microwave unit and system incorporating the unit are provided for use in tissue processing and other chem. reactions. The microwave unit is comprised of an energy source, a waveguide transmitting the microwave energy to a reaction chamber, and the reaction chamber being adapted to perform the desired chem. reaction. The unit provides gentle and uniform heating, with minimal heat loss and escape of volatile chems. The system may be operated continuously or batchwise, by manual operation or automatically. Preferably, an automated system is operated with continuous throughput using a robotic armature to obtain the advantages of the invention.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 101 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:453342 CAPLUS
DOCUMENT NUMBER: 135:43089
TITLE: Rapid tissue processor incorporating improved microwave unit
INVENTOR(S): Essenfeld, Ervin; Essenfeld, Harold; Morales, Azorides R.; Kimrey, Harold D.
PATENT ASSIGNEE(S): University of Miami, USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001044783 | A1 | 20010621 | WO 2000-US33760 | 20001214 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1238256 | A1 | 20020911 | EP 2000-990212 | 20001214 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003517601 | T2 | 20030527 | JP 2001-545824 | 20001214 |

PRIORITY APPLN. INFO.: US 1999-170545P P 19991214
WO 2000-US33760 W 20001214

AB An improved microwave unit and tissue processor system incorporating the unit are provided for use in rapid tissue processing. The microwave unit may be comprised of an energy source, a waveguide transmitting the microwave energy to a reaction chamber, and the reaction chamber being adapted to process tissue specimens for histol. The unit provides gentle and uniform heating, with minimal heat loss and escape of volatile chems. The system may be operated continuously and/or batchwise, by manual operation or automatically. The automated system may be operated with continuous throughput to obtain the advantages of the invention such as, for example, rapid processing under two hours and/or preservation of cell structure and tissue architecture. The processed tissue sections showed better antigen reactivity in immunohistochem. staining reactions.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 102 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:360291 CAPLUS
DOCUMENT NUMBER: 134:361826
TITLE: Methods for identifying and using **amyloid** -inhibitory compounds
INVENTOR(S): Petanesca, Suzana; Gandy, Sam; Frail, Donald E.
PATENT ASSIGNEE(S): American Home Products Corporation, USA; Research Foundation for Medical Hygiene
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001035106 | A2 | 20010517 | WO 2000-US30310 | 20001103 |
| WO 2001035106 | A3 | 20021114 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1272853 | A2 | 20030108 | EP 2000-976880 | 20001103 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003522737 | T2 | 20030729 | JP 2001-536585 | 20001103 |

PRIORITY APPLN. INFO.: US 1999-163819P P 19991105
WO 2000-US30310 W 20001103

AB The present invention relates to identification of agents that play a role in regulating brain **amyloid**-.beta. (A.beta.) levels in vivo. The invention provides compds. and methods of using such compds. to treat amyloidogenic conditions. It also provides a useful animal model for screening for and evaluating candidate **amyloid** inhibiting or therapeutic compds. In particular, ovariectomy (ovx) and **estrogen** replacement were found to affect brain A.beta. levels in guinea pigs. Long-term ovx of guinea pigs resulted in increased levels of total brain A.beta., as compared to intact animals, and the A.beta.42/A.beta.40 ratio was also elevated. Treatment of ovx guinea pigs with .beta.17-estradiol for ten days partially reversed the ovx-assocd. increase in brain A.beta. levels.

L1 ANSWER 103 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:338762 CAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001032928 | A2 | 20010510 | WO 2000-US30474 | 20001103 |
| WO 2001032928 | A3 | 20020725 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105

US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to det. the hypersensitivity of individuals to a given agent, such as drug or other chem., in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes assocd. with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes assocd. with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes assocd. with hypersensitivity. The expression of the genes predetd. to be assocd. with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and app. useful for identifying hypersensitivity in a subject are also disclosed.

L1 ANSWER 104 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:320155 CAPLUS
DOCUMENT NUMBER: 134:339182
TITLE: Alzheimer's disease diagnosis by genotyping apolipoprotein E allele and checking **estrogen** level, and its **estrogen** replacement therapy
INVENTOR(S): Einstein, Gillian; Shaughnessy, Laura W.; Schmechel, Donald E.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001031064 | A2 | 20010503 | WO 2000-US41177 | 20001016 |
| WO 2001031064 | A3 | 20020530 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002098481 | A1 | 20020725 | US 1999-425650 | 19991022 |
| US 6432643 | B2 | 20020813 | | |
| US 2002192725 | A1 | 20021219 | US 2002-180669 | 20020626 |

PRIORITY APPLN. INFO.: US 1999-425650 A 19991022

AB A method of screening a subject for risk of developing Alzheimer's disease comprises detg. the presence of at least one ApoE4 allele in a subject, and detg. the presence or absence of decreased **estrogen** levels in said subject (e.g., due to previous or impending menopause or hysterectomy). The methods involve detecting the presence or absence of an apolipoprotein E type 4 (ApoE4) isoform or DNA encoding ApoE4 in the subject by isoelec. focusing, immunoassay, or DNA amplification. The presence of at least one ApoE4 allele (and particularly two ApoE4 alleles)

in combination with decreased **estrogen** levels in said subject indicating said subject is at greater risk of developing Alzheimer's disease (e.g., as compared to subjects with at corresponding no. of ApoE4 alleles, but who do not have decreased **estrogen** levels). The subject will receive greater benefit from **estrogen** replacement therapy in treating Alzheimer's disease than a subject who does not carry one or two ApoE4 alleles.

L1 ANSWER 105 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:266004 CAPLUS
DOCUMENT NUMBER: 135:40282
TITLE: Experimental approaches and drugs in development for the treatment of dementia
AUTHOR(S): Emre, Murat; Qizilbash, Nawab
CORPORATE SOURCE: Department of Neurology, Istanbul Medical School, Istanbul, 34390, Turk.
SOURCE: Expert Opinion on Investigational Drugs (2001), 10(4), 607-617
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 101 refs. Treatment of dementia can be divided as symptomatic treatment of cognitive or non-cognitive symptoms and the treatment of underlying pathol. In the last decade the thrust of symptomatic treatment of Alzheimer's disease (AD) has been enhancement of cholinergic transmission. Besides the acetycholinesterase inhibitors (AChE-I) currently in use, cholinergic agonists and enhancers are in development. Other therapeutic approaches directed towards neurotransmitter substitution or modulation include serotoninergic, noradrenergic substances, neuropeptides and those acting via excitatory amino acid receptors, such as ampakines or NMDA antagonists. Introduction of atypical neuroleptics represents the most recent development in the treatment of behavioral symptoms. Efforts to treat the underlying pathol. are based on modulation of APP processing in order to decrease the accumulation of .beta.-**amyloid**, those to decrease tau hyperphosphorylation, use of nerve growth factors and those based on Apo-E modulation. Potential use of **estrogens** and NSAIDs are also under investigation. Recently, vaccination with **amyloid**-.beta. peptide has been reported to be effective in an animal model of AD, this putative vaccine is now in clin. trials. Likewise, recent studies suggest that some statins may have a prophylactic effect.
REFERENCE COUNT: 101 THERE ARE 101 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 106 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:265645 CAPLUS
DOCUMENT NUMBER: 134:292402
TITLE: Methods for identifying RNA binding compounds
INVENTOR(S): Rana, Tariq M.
PATENT ASSIGNEE(S): University of Medicine and Dentistry, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001025486 | A1 | 20010412 | WO 2000-US27389 | 20001004 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| EP 1218544 | A1 | 20020703 | EP 2000-968684 | 20001004 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL | | | | |
| US 6420591 | B1 | 20020716 | US 2000-679728 | 20001004 |
| US 6503713 | B1 | 20030107 | US 2000-679451 | 20001004 |
| US 6583309 | B1 | 20030624 | US 2002-151800 | 20020521 |
| US 2003153523 | A1 | 20030814 | US 2002-295761 | 20021115 |

PRIORITY APPLN. INFO.:
US 1999-157646P P 19991004
US 2000-679451 A1 20001004
US 2000-679728 A3 20001004
WO 2000-US27389 W 20001004

AB The present invention relates to methods of screening for compds. that bind RNA mols. In particular, the methods of the invention comprise screening a library of test compds., each of which is attached to a solid support, with a dye-labeled RNA mol. to form a dye-labeled target RNA: support-attached test compd. complex. By virtue of the dye label on the target RNA, the support becomes labeled and can be sepd. from unlabeled solid supports. The present invention further relates to methods of inhibiting an RNA-protein interaction, to methods of screening for compds. that increase or decrease the prodn. of a protein, and to methods of screening for a compd. that is capable of treating or preventing a disease whose progression is assocd. with an in vivo binding of a test compd. to a target RNA.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 107 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:246515 CAPLUS
DOCUMENT NUMBER: 134:261267
TITLE: .alpha.-Sulfonylaminohydroxamic acid inhibitors of matrix metalloproteinases for the treatment of peripheral or central nervous system disorders
INVENTOR(S): Sahagan, Barbara Gail; Villalobos, Anabella
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 26 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| EP 1088550 | A1 | 20010404 | EP 2000-308442 | 20000927 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| US 6417229 | B1 | 20020709 | US 2000-671435 | 20000927 |
| ZA 2000005217 | A | 20020328 | ZA 2000-5217 | 20000928 |
| JP 2001097854 | A2 | 20010410 | JP 2000-298071 | 20000929 |

PRIORITY APPLN. INFO.:
US 1999-157083P P 19991001
OTHER SOURCE(S): MARPAT 134:261267

AB A method is provided for using the title compds., pharmaceutically acceptable salts thereof, or pharmaceutical compns. thereof, in the

treatment of a disease, condition or disorder of the peripheral or central nervous system, including but not limited to Alzheimer's disease, stroke/cerebral ischemia, head trauma, spinal cord injury, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, migraine, cerebral **amyloid** angiopathy, AIDS, age-related cognitive decline, mild cognitive impairment and prion diseases.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 108 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:219930 CAPLUS
DOCUMENT NUMBER: 134:305517
TITLE: Neuroprotective effects of **estrogen** against beta-**amyloid** toxicity are mediated by **estrogen** receptors in cultured neuronal cells
AUTHOR(S): Kim, H.; Bang, O. Y.; Jung, M. W.; Ha, S. D.; Hong, H. S.; Huh, K.; Kim, S. U.; Mook-Jung, I.
CORPORATE SOURCE: Brain Disease Research Center, Ajou University School of Medicine, Suwon, 442-721, S. Korea
SOURCE: Neuroscience Letters (2001), 302(1), 58-62
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although **estrogen** is known to exert beneficial effects on Alzheimer's disease, its underlying cellular mechanisms have not been clear. In this study the authors investigated whether or not neuroprotective effects of **estrogen** are mediated by **estrogen** receptors (ERs). Treatment of **estrogen** (1.8 nM) reduced beta-**amyloid** (A.beta.)-induced death of ER-expressing W4 cells. This effect of **estrogen** was blocked by a specific ER blocker ICI 182,780. When **estrogen** was added to HT22 cells, which lack functional ERs, A.beta.-induced cell death was not affected. Transfection of HT22 cells with human ER.alpha., but not ER.beta., restored protective action of **estrogen** against A.beta.. Hoechst staining revealed that **estrogen** protected ER.alpha.-expressing cells by blocking A.beta.-induced apoptosis. These results indicate that **estrogen** blocks A.beta.-induced cell death via ER.alpha.-dependent pathways.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 109 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:170162 CAPLUS
DOCUMENT NUMBER: 135:340013
TITLE: Ulcerative colitis and Crohn's disease: distinctive gene expression profiles and novel susceptibility candidate genes
AUTHOR(S): Lawrance, Ian C.; Fiocchi, Claudio; Chakravarti, Shukti
CORPORATE SOURCE: Department of Medicine, Case Western Reserve University School of Medicine, University Hospitals of Cleveland, Cleveland, OH, USA
SOURCE: Human Molecular Genetics (2001), 10(5), 445-456
CODEN: HMGEE5; ISSN: 0964-6906
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To elucidate the biol. dysregulation underlying two forms of inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD), the authors examd. global gene expression profiles of inflamed colonic tissue

using DNA microarrays. Our results identified several genes with altered expression not previously linked to IBD. In addn. to the expected upregulation of various cytokine and chemokine genes, novel immune function-related genes such as IGHG3, IGLL2 and CD74, inflammation-related lipocalins HNL and NGAL, and proliferation-related GRO genes were over-expressed in UC. Certain cancer-related genes such as DD96, DRAL and MXI1 were differentially expressed only in UC. Other genes over-expressed in both UC and CD included the REG gene family and the calcium-binding S100 protein genes S100A9 and S100P. The natural antimicrobial defensin DEFA5 and DEFA6 genes were particularly over-expressed in CD. Overall, significant differences in the expression profiles of 170 genes identified UC and CD as distinct mol. entities. The genomic map locations of the dysregulated genes may identify novel candidates for UC and CD genetic susceptibility.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 110 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:138023 CAPLUS

DOCUMENT NUMBER: 135:431

TITLE: The neuroprotective effects of phytoestrogens on **amyloid** .beta. protein-induced toxicity are mediated by abrogating the activation of caspase cascade in rat cortical neurons

AUTHOR(S): Wang, Chuen-Neu; Chi, Chih-Wen; Lin, Yun-Lian; Chen, Chieh-Fu; Shiao, Young-Ji

CORPORATE SOURCE: National Research Institute of Chinese Medicine, Taipei, 112, Taiwan

SOURCE: Journal of Biological Chemistry (2001), 276(7), 5287-5295
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Amyloid** .beta. protein (A.beta.) elicits a toxic effect on neurons in vitro and in vivo. In present study we attempt to elucidate the mechanism by which A.beta. confers its neurotoxicity. The neuroprotective effects of phytoestrogens on A.beta.-mediated toxicity were also investigated. Cortical neurons treated with 5 .mu.M A.beta.-(25-35) for 40 h decreased the cell viability by 45.5.+-.4.6% concomitant with the appearance of apoptotic morphol. 50 .mu.M kaempferol and apigenin decreased the A.beta.-induced cell death by 81.5.+-.9.4% and 49.2.+-.9.9%, resp. A.beta. increased the activity of caspase 3 by 10.6-fold and to a lesser extent for caspase 2, 8, and 9. The A.beta.-induced activation of caspase 3 and release of cytochrome c showed a biphasic pattern. Apigenin abrogated A.beta.-induced cytochrome c release, and the activation of caspase cascade. Kaempferol showed a similar effect but to a less extent. Kaempferol was also capable of eliminating A.beta.-induced accumulation of reactive oxygen species. These two events accounted for the remarkable effect of kaempferol on neuroprotection. Quercetin and probucol did not affect the A.beta.-mediated neurotoxicity. However, they potentiated the protective effect of apigenin. Therefore, these results demonstrate that A.beta. elicited activation of caspase cascades and reactive oxygen species accumulation, thereby causing neuronal death. The blockade of caspase activation conferred the major neuroprotective effect of phytoestrogens. The antioxidative activity of phytoestrogens also modulated their neuroprotective effects on A.beta.-mediated toxicity.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 111 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:80292 CAPLUS
DOCUMENT NUMBER: 134:203595
TITLE: The environmental estrogenic compound bisphenol A exerts estrogenic effects on mouse hippocampal (HT-22) cells: neuroprotection against glutamate and **amyloid** beta protein toxicity
AUTHOR(S): Gursoy, Erdal; Cardounel, Arturo; Kalimi, Mohammed
CORPORATE SOURCE: Department of Physiology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA, 23298-0551, USA
SOURCE: Neurochemistry International (2001), 38(2), 181-186
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have examd. using immortalized clonal mouse hippocampal cell line (HT-22) whether the environmental estrogenic compd. bisphenol A (BPA), like **estrogen**, has any neuroprotective effect against glutamate and **amyloid** beta protein-induced neurotoxicity. BPA protects HT-cells against both 5 mM glutamate and 2 .mu.M **amyloid** beta protein-induced cell death in a dose dependent manner. Optimum protection was attained at 1 .mu.M and 500 nM BPA against 5 mM glutamate and 2 .mu.M **amyloid** beta protein-induced HT-22 cell death, resp. Using confocal immunoflourescence microscopy technique, we obsd. that 20 h of treatment with 5 mM glutamate resulted in intense nuclear localization of the glucocorticoid receptors (GR) in HT-22 cells as compared to control untreated cells. Interestingly, 1 .mu.M BPA treatment for 24 h, followed by 20-h treatment with 5 mM glutamate, resulted in dramatic redn. in GR nuclear localization. We conclude that: (i) BPA mimics **estrogen** and exerts neuroprotective effects against both neurotoxins used; (ii) BPA inhibits enhanced nuclear localization of GR induced by glutamate; and (iii) HT-22 cells provide a good in vitro model system for screening the potencies of various environmental compds. for their estrogenic activity.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 112 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:56199 CAPLUS
DOCUMENT NUMBER: 134:231976
TITLE: **Estrogen** and Raloxifene activities on **amyloid**-.beta.-induced inflammatory reaction
AUTHOR(S): Thomas, Tom; Bryant, Margie; Clark, Linda; Garces, Amanda; Rhodin, Johannes
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, 33612, USA
SOURCE: Microvascular Research (2001), 61(1), 28-39
CODEN: MIVRA6; ISSN: 0026-2862
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The prevalence of Alzheimer's disease (AD) in women is double that of men. Several studies indicate that use of **estrogen** after menopause by women may reduce the risk of developing AD. The risk of **estrogen** -dependent tumors assocd. with **estrogen** replacement therapy has prompted the use of alternatives, like the SERM raloxifene, which exert **estrogen** agonist effects on selected target tissues. Whether SERMS provide cognitive and cardiovascular benefits comparable to those of **estrogens** is an active area of investigation in women's health. A chronic inflammatory process is central to the pathol. of Alzheimer's disease. Using an animal model the authors compared the anti-inflammatory activity of orally administered **estrogens** (2 mg/kg) and

raloxifene (3 mg/kg) in ovariectomized rats. Morphol. anal. of A.beta.(1-40)-induced inflammatory reaction featured adhesion and transmigration of leukocytes across the vessel wall, endothelial disruption, and platelet activation. **Estrogen** showed remarkable anti-inflammatory action, whereas raloxifene had no significant beneficial effect. Inhibition of the inflammatory process may contribute to the reported efficacy of **estrogen** in the treatment of AD. (c) 2001 Academic Press.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 113 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:51525 CAPLUS
DOCUMENT NUMBER: 135:116248
TITLE: Approach towards an integrative drug treatment of Alzheimer's disease
AUTHOR(S): Windisch, M.
CORPORATE SOURCE: JSW-Research Forschungslabor, Graz, Austria
SOURCE: Journal of Neural Transmission, Supplement (2000), 59(Advances in Dementia Research), 301-313
CODEN: JNTSD4; ISSN: 0303-6995
PUBLISHER: Springer-Verlag Wien
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 98 refs. At present pharmacotherapy of Alzheimer's disease (AD) is limited to acetylcholinesterase inhibitors. These drugs produce small, but consistent improvements of memory and global function, some are also pos. influencing activities of daily living. This therapeutic approach neglects the complexity of AD and the fact that most of the degenerating neurons are not cholinergic. Acetylcholinesterase inhibitors are symptomatic drugs, with no influence on disease progression. There is a need for disease modifying compds., or preventive drugs. Data are indicating that vitamin E has some ability to influence the disease progression. The potency of non-steroidal anti-inflammatory drugs (NSAIDs) or **estrogen** as preventive agents has to be explored further in prospective clin. studies. The initial hope in the use of naturally occurring neurotrophic factors, like nerve growth factor, to rescue cholinergic neurons from degeneration and to restore cognitive function has been disappointed in first, small clin. studies. The peptidergic drug Cerebrolysin exhibiting neurotrophic stimulation, neuroimmunotrophic regulation and induction of BBB glucose transporter expression, might be able to address the pathol. changes of AD at different levels simultaneously. In addn. to an impressive preclin. database, results from 3 placebo-controlled, double-blind studies demonstrate significant improvements of cognitive performance, global function and activities of daily living in AD patients. In all studies persisting improvements, up to 6 mo after drug withdrawal, indicate a powerful disease modifying activity.

REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 114 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:51519 CAPLUS
DOCUMENT NUMBER: 135:101729
TITLE: Present and future of Alzheimer therapy
AUTHOR(S): Giacobini, E.
CORPORATE SOURCE: Department of Geriatrics, University Hospitals of Geneva, Thonex-Geneva, Switz.
SOURCE: Journal of Neural Transmission, Supplement (2000), 59(Advances in Dementia Research), 231-242
CODEN: JNTSD4; ISSN: 0303-6995
PUBLISHER: Springer-Verlag Wien

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 36 refs. Different major lines of drugs have been developed or are under development for the treatment of Alzheimer Disease (AD): cholinergic drugs (mainly cholinesterase inhibitors), anti-.beta.-**amyloid** drugs, **estrogens** and anti-inflammatories. Cholinesterase inhibitors are the only drugs presently approved in the USA and Europe for the indication of AD. Cholinesterase inhibitors tested in clin. trials in Europe, the USA and Japan include .ltoreq.10 drugs; however, most of these compds. have advanced to Phase III clin. trials. Based on results related to a population of >8000 patients it is concluded that several of these compds. have shown significant clin. efficacy and safety in the treatment of AD. There are, however, differences with regard to side effects. The major clin. effect is stabilization of cognitive function during a 6-12-mo period, with a parallel improvement of behavioral symptoms. A long-term effect of cholinesterase inhibitors extending to 2 yr has been reported. Future uses of these drugs are treatment of other types dementias such as Lewy body dementia, vascular dementia and Down's Syndrome dementia. Combination of cholinesterase inhibitors with **estrogens**, antioxidants and anti-inflammatories may represent a further improvement of therapy. From the economics point of view, treatment with cholinesterase inhibitors is not cost neutral.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 115 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:13030 CAPLUS
DOCUMENT NUMBER: 134:217233
TITLE: **Estrogen** protection of cerebral ischemia
AUTHOR(S): Me, Dongai; Zhang, Xiaoqin; Zhang, Junjian
CORPORATE SOURCE: No. 2 Hospital, Hubei Univ. Medical Sciences, Wuhan, 430071, Peop. Rep. China
SOURCE: Zhonghua Shenjingke Zazhi (2000), 33(4), 247-248
CODEN: ZSZAFN; ISSN: 1006-7876
PUBLISHER: Zhonghua Yixuehui Zazhishe
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review with 19 refs., on mechanisms of **estrogen** protection of cerebral ischemia, via promotion of cerebral circulation; suppression of excitatory amino acid transmitter toxicity; vasodilatation; and suppression of .beta.-**amyloids** formation.

L1 ANSWER 116 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:368 CAPLUS
DOCUMENT NUMBER: 135:72051
TITLE: The mouse brain transcriptome by SAGE: Differences in gene expression between P30 brains of the partial Trisomy 16 mouse model of down syndrome (Ts65Dn) and normals
AUTHOR(S): Chrast, Roman; Scott, Hamish S.; Papasavvas, Marie Pierre; Rossier, Colette; Antonarakis, Emmanuel S.; Barras, Christine; Davisson, Muriel T.; Schmidt, Cecilia; Estivill, Xavier; Dierssen, Mara; Pritchard, Melanie; Antonarakis, Stylianos E.
CORPORATE SOURCE: Division of Medical Genetics and Graduate Program of Cellular and Molecular Biology, Geneva University Medical School and University Hospital, Geneva, Switz.
SOURCE: Genome Research (2000), 10(12), 2006-2021
CODEN: GEREFS; ISSN: 1088-9051
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Trisomy 21, or Down syndrome (DS), is the most common genetic cause of mental retardation. Changes in the neuropathol., neurochem., neurophysiol., and neuropharmacol. of DS patients' brains indicate that there is probably abnormal development and maintenance of central nervous system structure and function. The segmental trisomy mouse (Ts65Dn) is a model of DS that shows analogous neurobehavioral defects. We have studied the global gene expression profiles of normal and Ts65Dn male and normal female mice brains (P30) using the serial anal. of gene expression (SAGE) technique. From the combined sample we collected a total of 152,791 RNA tags and obsd. 45,856 unique tags in the mouse brain transcriptome. There are 14 ribosomal protein genes (nine underexpressed) among the 330 statistically significant differences between normal male and Ts65Dn male brains, which possibly implies abnormal ribosomal biogenesis in the development and maintenance of DS phenotypes. This study contributes to the establishment of a mouse brain transcriptome and provides the first overall anal. of the differences in gene expression in aneuploid vs. normal mammalian brain cells.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 117 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:875392 CAPLUS

DOCUMENT NUMBER: 134:157765

TITLE: Ovariectomy and 17.beta.-estradiol modulate the levels of Alzheimer's **amyloid** .beta. peptides in brain

AUTHOR(S): Petanceska, S. S.; Nagy, V.; Frail, D.; Gandy, S.

CORPORATE SOURCE: Nathan Kline Institute, Orangeburg, NY, 10962, USA

SOURCE: Experimental Gerontology (2000), 35(9-10), 1317-1325
CODEN: EXGEAB; ISSN: 0531-5565

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Alzheimers's disease (AD) is a neurodegenerative disorder characterized by accumulation of aggregated forms of the 40- and 42-amino acid A.beta. peptides (A.beta.40 and A.beta.42). **Estrogen** replacement therapy (ERT) in postmenopausal women is assocd. with decreased risk for AD and/or delay in disease onset. The mechanism by which **estrogen** exerts this neuroprotective effect is elusive. 17.beta.-Estradiol (E2) was shown to reduce the release of A.beta. peptides by primary neuronal cultures of murine and human origin. To test whether **estrogen** can modulate the metab. of A.beta. peptides in vivo, four exptl. sets of guinea pigs were used: intact animals, ovariectomized animals, and ovariectomized animals that received E2 at two different doses. Ovariectomy was assocd. with a 1.5-fold av. increase in total brain A.beta. levels as compared to intact controls. E2 treatment significantly reversed the ovariectomy-induced increase in brain A.beta. levels. The high-dose E2 treatment did not lead to further decrease in brain A.beta. beyond the one obsd. with the low-dose E2 treatment. The authors' results infer that cessation of ovarian **estrogen** prodn. in postmenopausal women might facilitate A.beta. deposition by increasing the local concns. of A.beta.40 and A.beta.42 peptides in brain and suggest that modulation of A.beta. metab. may be one of the ways by which ERT prevents and/or delays the onset of AD in postmenopausal women.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 118 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:834997 CAPLUS

DOCUMENT NUMBER: 134:66348

TITLE: Testosterone stimulates rapid secretory **amyloid** precursor protein release from rat

hypothalamic cells via the activation of the mitogen-activated protein kinase pathway

AUTHOR(S): Goodenough, S.; Engert, S.; Behl, C.

CORPORATE SOURCE: Independent Research Group Neurodegeneration, Max Planck Institute of Psychiatry, Munich, D-80804, Germany

SOURCE: Neuroscience Letters (2000), 296(1), 49-52
CODEN: NELED5; ISSN: 0304-3940

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The processing of the **amyloid** precursor protein (APP) has become a major focus of research into Alzheimer's disease (AD). Recently, repeated doses of testosterone have been shown to enhance the secretion of the product of the .alpha.-cleavage pathway of APP (sAPP.alpha.) over a period of days. Here, the time course of secretion of sAPP.alpha. after a single physiol. dose of testosterone using an immortalized rat hypothalamic cell line (GT1-7) and the signaling pathways involved was analyzed. Testosterone was found to increase the amt. of APP secretion rapidly after treatment without effecting the overall amt. of cellular APP. The species of APP secreted was found to be predominantly the product of the non-amyloidogenic .alpha.-secretory pathway. Further, this event is regulated via aromatase-mediated conversion of testosterone to **estrogen** and the mitogen-activated protein kinase (MAP kinase) signaling pathway. Taken together these data partially elucidates the cellular cascade by which testosterone stimulates sAPP secretion.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 119 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:790616 CAPLUS

DOCUMENT NUMBER: 133:334062

TITLE: Method for diminishing specific immune reactions by blocking the function of receptors for costimulators

INVENTOR(S): Sheriff, Ahmed; Gebauer, Frank

PATENT ASSIGNEE(S): Germany

SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000066715 | A1 | 20001109 | WO 2000-EP3984 | 20000504 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1085085 | A1 | 20010321 | EP 1999-118518 | 19990918 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| DE 19944858 | A1 | 20010329 | DE 1999-19944858 | 19990918 |
| EP 1173550 | A1 | 20020123 | EP 2000-936709 | 20000504 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |

JP 2002542819 T2 20021217 JP 2000-615740 20000504
PRIORITY APPLN. INFO.: DE 1999-19920412 A 19990504
DE 1999-19944858 A 19990918
EP 1999-118518 A 19990918
WO 2000-EP3984 W 20000504

AB The invention relates to an antigen-presenting cell which mainly presents predetd. antigens (monoantigenic antigen-presenting cell) and which is characterized in that the monoantigenic antigen-presenting cell is capable of dividing and one of the functions of co-stimulator receptors such as a B7 or CD40 receptor is suppressed. This is achieved by introducing a gene for an autoantigen into the antigen presenting cells. Intracellular presentation of the autoantigen blocks transfer of the coreceptor to the cell surface, leading to a cessation of proliferation of helper T-cells and their death. In addn., these cells may have elevated levels of a homing receptor such as CD44 that helps to improve rates of migration to lymph nodes and of proliferation.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 120 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:756915 CAPLUS
DOCUMENT NUMBER: 133:318255
TITLE: Troglitazone-responsive liver genes and method of screening for hepatotoxicity
INVENTOR(S): Gould-Rothberg, Bonnie E.; DiPippo, Vincent A.
PATENT ASSIGNEE(S): Curagen Corporation, USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000063435 | A2 | 20001026 | WO 2000-US10076 | 20000414 |
| WO 2000063435 | A3 | 20020912 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1169481 | A1 | 20020109 | EP 2000-923362 | 20000414 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2003513613 | T2 | 20030415 | JP 2000-612512 | 20000414 |

PRIORITY APPLN. INFO.: US 1999-129763P P 19990415
US 1999-156924P P 19990928
US 2000-548589 A 20000413
WO 2000-US10076 W 20000414

AB Disclosed are methods of identifying toxic agents, e.g. , hepatotoxic agents, using differential gene expression. Also disclosed are novel nucleic acid sequences whose expression is differentially regulated by troglitazone. Thus, 169 rat liver genes whose expression was altered by exposure to troglitazone were identified (and the GenBank accession no. provided). Twenty-one of these genes were novel; the remainder had been previously reported.

L1 ANSWER 121 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:755099 CAPLUS
DOCUMENT NUMBER: 134:206129
TITLE: Pregnancy and amyloidosis: II. Suppression of amyloidogenesis during pregnancy
AUTHOR(S): Shtrasburg, Shmuel; Pras, Mordechai; Dolitzky, Mordechai; Pariente, Clara; Gal, Rivka; Livneh, Avi
CORPORATE SOURCE: Heller Institute of Medical Research, Sheba Medical Center, Tel-Hashomer, 52621, Israel
SOURCE: Journal of Laboratory and Clinical Medicine (2000), 136(4), 314-319
CODEN: JLCMAK; ISSN: 0022-2143
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The observation of a deleterious effect of pregnancy on kidney function in amyloidosis of familial Mediterranean fever suggests that pregnancy may enhance amyloidogenesis. To det. whether pregnancy may indeed affect amyloidogenesis, pregnant mice were made amyloidotic by administration of **amyloid** enhancing factor (AEF) and AgNO3 at different points in time from conception, and **amyloid**- deposition was studied with the crush-and-smear technique. A possible effect of exogenous female sex hormones (.beta.-estradiol and progesterone) on amyloidogenesis was studied by administration of these hormones during **amyloid** induction in nonpregnant female mice. Amyloidogenesis was found to be significantly suppressed in mice during pregnancy. The redn. was possibly related to the effect of pregnancy on the inflammatory stimulus (AgNO3) and not on the administered AEF. Exogenous **estrogen** and progesterone failed to inhibit amyloidogenesis in nonpregnant mice. These findings suggest that pregnancy may suppress amyloidogenesis in mice. The suppression is caused by an anti-inflammatory effect of pregnancy. **Estrogen** and progesterone are probably unrelated to this finding.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 122 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:675641 CAPLUS
DOCUMENT NUMBER: 133:329781
TITLE: **Estrogen** enhances uptake of **amyloid** .beta.-protein by microglia derived from the human cortex
AUTHOR(S): Li, Rena; Shen, Yong; Yang, Li-Bang; Lue, Lih-Fen; Finch, Caleb; Rogers, Joseph
CORPORATE SOURCE: Sun Health Research Institute, Sun City, AZ, 85351, USA
SOURCE: Journal of Neurochemistry (2000), 75(4), 1447-1454
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In recent years, inflammatory mechanisms have been increasingly appreciated as important steps in the pathol. of Alzheimer's disease (AD). There are two pathol. defects in AD: chronic inflammation and impaired clearance of **amyloid** .beta.-peptide (A.beta.). In the periphery, **estrogen** both increases macrophage phagocytosis and has antiinflammatory effects. If **estrogen** had a similar effect in the CNS, it could reverse inflammatory defects in AD. Although microglia are a key component of the immune system and help clear A.beta. deposits in the AD brain, little is known about the effects of **estrogen** on CNS microglia. Therefore, we sought to det. the relationship between **estrogen** treatment and internalization of A.beta. by microglia by quantifying the internalization of aggregated

A.beta. by human cortical microglia. A.beta. uptake was found to be dose- and time-dependent in cultured microglia. Increased A.beta. uptake was obsd. at 1.5 and 24 h after addn. of aggregated A.beta. (50, 100, or 1,000 nM A.beta.), and this uptake was enhanced by pretreatment with **estrogen**. The expression of **estrogen** receptor (ER) .beta. (ER-.beta.) was also up-regulated by **estrogen** treatment. Cells cotreated with ICI 182,780, an ER antagonist, showed significantly reduced internalization of A.beta. in cultured microglia. These results indicate that microglia express an ER-.beta. but that the effect of **estrogen** on enhancing clearance of A.beta. may be related to the receptor-independent action of **estrogen** or to nonclassical ER effects of **estrogen**. Thus, stimulation of the ER might contribute to the therapeutic action of **estrogen** in the treatment of AD.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 123 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:591201 CAPLUS
DOCUMENT NUMBER: 134:205567
TITLE: Post-menopausal **estrogen** deprivation and Alzheimer's disease
AUTHOR(S): Gandy, S.; Duff, K.
CORPORATE SOURCE: Nathan S. Kline Institute for Psychiatric Research, Department of Psychiatry, New York University, Orangeburg, NY, 10962, USA
SOURCE: Experimental Gerontology (2000), 35(4), 503-511
CODEN: EXGEAB; ISSN: 0531-5565
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 28 refs. **Estrogen** deprivation has been implicated as a risk factor in Alzheimer's disease (AD) as epidemiol. data suggests that **estrogen** replacement therapy can protect against the onset, and progression of the disease. Biochem. data suggests that **estrogen** exerts its affect through the processing of the **amyloid** precursor protein to beta-**amyloid** which is deposited in the brains of patients with AD. The effects of **estrogens** may be more widespread, however, as it has been implicated in the maintenance of neuronal architecture and protection from free radicals. This review aims to discuss the various roles of **estrogen** in the development of AD.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 124 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:584126 CAPLUS
DOCUMENT NUMBER: 133:246690
TITLE: The aging process: where are the drug opportunities?
AUTHOR(S): Smith, Roy G.
CORPORATE SOURCE: Huffington Center on Aging and Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Current Opinion in Chemical Biology (2000), 4(4), 371-376
CODEN: COCBF4; ISSN: 1367-5931
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 50 refs. New data support a role for growth hormone secretagogue receptor agonists as rejuvenating agents. Two enzymes crit. for the formation of .beta.-**amyloid** plaques in Alzheimer's

disease have been identified. **Estrogen** receptor .beta. continues to emerge as a potential drug target. The orphan nuclear receptor Nurr1 appears to be a target for treatment of Parkinson's disease, and proparglyamines are emerging as inhibitors of oxidative damage in neurons.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 125 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:510507 CAPLUS
DOCUMENT NUMBER: 133:217890
TITLE: Ovariectomy and 17.beta.-estradiol modulate the levels of Alzheimer's **amyloid** .beta. peptides in brain
AUTHOR(S): Petanceska, Suzana S.; Nagy, Vanja; Frail, Donald; Gandy, Sam
CORPORATE SOURCE: New York University at Nathan Kline Institute, Orangeburg, NY, USA
SOURCE: Neurology (2000), 54(12), 2212-2217
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To test whether female gonadal hormone status and **estrogen** modulate the metab. A.beta. peptides in vivo. AD is a neurodegenerative disorder characterized by accumulation of aggregated of the 40- and 42-amino acid A.beta. peptides (A.beta.40 and A.beta.42). **Estrogen** replacement therapy in postmenopausal women assocd. with decreased risk for AD or delay in disease onset or both. The mechanism by which **estrogen** exerts neuroprotective effect is elusive. 17.beta.-Estradiol (E2) was shown to reduce the release of A.beta. peptides by primary neuronal cultures of murine and human origin. For this purpose, four exptl. sets of guinea pigs were used: animals, ovariectomized animals (ovx), and ovariectomized animals that received E2 at two different doses (ovx+low- E2 and ovx+high-dose E2). Brain A.beta.40 and A.beta.42 levels were assessed using A.beta.40 and A.beta.42-specific ELISA. Prolonged ovariectomy resulted in uterine atrophy and decreased serum E2 levels and was assocd. with pronounced increase in brain A.beta. levels. Total brain A.beta. in the ovx animals was increased by 1.5-fold on av. compared to intact controls. E2 treatment of ovariectomized animals led to uterine hypertrophy and a dose-dependent increase in serum E2 levels. In addn., both doses of E2 significantly reversed the ovariectomy-induced increase in A.beta. levels. The high-dose E2 treatment did not lead to a further decrease in brain A.beta. beyond that obsd. with low-dose E2 treatment. Our results infer that cessation of ovarian **estrogen** prodn. in postmenopausal women might facilitate A.beta. deposition by increasing the local concns. of A.beta.40 and A.beta.42 peptides in brain. Addn., our finding that E2 treatment is assocd. with diminution of brain A.beta. levels suggests that modulation of metab. may be one of the ways by which **estrogen** replacement therapy prevents or delays the onset of AD or both in postmenopausal women.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 126 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:507728 CAPLUS
DOCUMENT NUMBER: 133:265063
TITLE: V642I APP-Inducible Neuronal Cells: A Model System for Investigating Alzheimer's Disorders
AUTHOR(S): Niikura, Takako; Murayama, Norie; Hashimoto, Yu-ichi; Ito, Yuko; Yamagishi, Yohichi; Matsuoka, Masaaki;

Takeuchi, Yuji; Aiso, Sadakazu; Nishimoto, Ikuo
CORPORATE SOURCE: Department of Pharmacology and Neurosciences, KEIO University School of Medicine, Tokyo, 160, Japan
SOURCE: Biochemical and Biophysical Research Communications (2000), 274(2), 445-454
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB APP is a precursor of .beta. **amyloid** deposited in Alzheimer's disease (AD). Although genetic studies established that mutations in APP cause familial AD (FAD), the mechanism for neuronal death by FAD mutants has not been well understood. We established neuronal cells (F11/EcR/V642I cells) in which V642I APP was inducibly expressed by ecdysone. Treatment with ecdysone, but not vehicle, killed most cells within a few days, with rounding, shrinkage, and detachment as well as nuclear fragmentation. Death was suppressed by Ac-DEVD-CHO and pertussis toxin. Electron microscopic anal. revealed that apoptosis occurred in ecdysone-treated cells. V642I-APP-induced death was suppressed by the anti-AD factors **estrogen** and apoE2. These data demonstrate not only that expression of this FAD gene causes neuronal apoptosis, but that F11/EcR/V642I cells, the first neuronal cells with inducible FAD gene expression, provide a useful model system in investigating AD disorders. (c) 2000 Academic Press.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 127 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:490372 CAPLUS
DOCUMENT NUMBER: 133:264615
TITLE: Regulation of Alzheimer .beta.-**amyloid** precursor trafficking and metabolism
AUTHOR(S): Gandy, S.; Petanceska, S.
CORPORATE SOURCE: Dep. Psychiatry, The Nathan S. Kline Inst. Psychiatric Res., New York Univ., Orangeburg, NY, 10962, USA
SOURCE: Biochimica et Biophysica Acta (2000), 1502(1), 44-52
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 51 refs. Alzheimer's disease (AD) is characterized by the intracranial accumulation of the 4 kDa **amyloid**-.beta. peptide (A.beta.), following proteolysis of a .apprx.700-amino acid, integral membrane precursor, the Alzheimer **amyloid** precursor protein (APP). The best evidence causally linking APP to AD has been provided by the discovery of mutations within the APP coding sequence that segregate with disease phenotypes in autosomal dominant forms of familial AD (FAD). Though FAD is rare (<10% of all AD), the hallmark features ( **amyloid** plaques, neurofibrillary tangles, synaptic and neuronal loss, neurotransmitter deficits and dementia) are indistinguishable when FAD is compared with typical, common, 'non-familial', or sporadic, AD (SAD). Studies of some clin. relevant mutant APP mols. from FAD families have yielded evidence that APP mutations can lead to the enhanced generation or aggregability of A.beta., consistent with a pathogenic role in AD. Other genetic loci for FAD have been discovered which are distinct from the immediate regulatory and coding regions of the APP gene, indicating that defects in mols. other than APP can also specify cerebral amyloidogenesis and FAD. To date, all APP and non-APP FAD mutations can be demonstrated to have the common feature of promoting amyloidogenesis of A.beta.. Epidemiol. studies indicate that postmenopausal women on **estrogen** replacement therapy (ERT) have their relative risk of developing SAD diminished by about one third as compared with age-matched

women not receiving ERT. Because of the key role of cerebral A.beta. accumulation in initiating AD pathol., it is most attractive that estradiol might modulate SAD risk or age-at-onset by inhibiting A.beta. accumulation. A possible mechanistic basis for such a scenario is reviewed here.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 128 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:487498 CAPLUS
DOCUMENT NUMBER: 133:361270
TITLE: Current biochemical hypotheses for Alzheimer's disease
AUTHOR(S): Rustad, Katrine Wangen
CORPORATE SOURCE: Division for Protection and Materiel, FFI (Norwegian Defence Research Establishment), Kjeller, N-2027, Norway
SOURCE: Current Topics in Neurochemistry (1999), 2, 53-65
CODEN: CTNEFZ
PUBLISHER: Research Trends
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 105 refs. Alzheimer's disease (AD) is a neurodegenerative disease with an etiol. that has not been fully elucidated. The pathol. is characterized by the presence of neurofibrillary tangles, senile plaques, deposition of **amyloid** beta peptide (A.beta.) and a selective loss of neurons replaced by decreased synaptic d. This histopathol. condition has several possible causes, including genetic defects, apoptosis, excitotoxicity, inflammatory mechanisms, altered zinc distribution in AD brain or effects linked to the female hormone **estrogen**. Lately, oxidative stress has received increasing interest as a possible cause of the neurodegeneration. All these topics are discussed in this review, together with altered signal transductions that are found in the Alzheimer-affected brain. Special attention is also given to the role of the glutamatergic system.

REFERENCE COUNT: 105 THERE ARE 105 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 129 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:460904 CAPLUS
DOCUMENT NUMBER: 133:187994
TITLE: Neuroprotective effects of **estrogens**: potential mechanisms of action
AUTHOR(S): Green, Pattie S.; Simpkins, James W.
CORPORATE SOURCE: Center for the Neurobiology of Aging and Department of Pharmacodynamics, University of Florida, Gainesville, FL, 32611, USA
SOURCE: International Journal of Developmental Neuroscience (2000), 18(4-5), 347-358
CODEN: IJDND6; ISSN: 0736-5748
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 151 refs. Epidemiol. studies assoc. post-menopausal **estrogen** use with a redn. in risk of Alzheimer's disease, a redn. in risk of Parkinson's disease, and death from stroke. The neuroprotective efficacy of **estrogens** have been well described and may contribute to these clin. effects. **Estrogen**-mediated neuroprotection has been described in several neuronal culture model systems with toxicities including serum-deprivation, .beta.-**amyloid**-induced toxicity, excitotoxicity, and oxidative stress. In animal models, **estrogens** have been shown to attenuate

neuronal death in rodent models of cerebral ischemia, traumatic injury, and Parkinson's disease. Although **estrogens** are known to exert several direct effects on neurons, the cellular mechanisms behind the neuroprotective efficacy of the steroid are only beginning to be elucidated. In this review, the authors summarize the data supporting a neuroprotective role for **estrogens** in both culture and animal models and discuss neuronal effects of **estrogens** that may contribute to the neuroprotective effects. These effects include activation of the nuclear **estrogen** receptor, altered expression of bcl-2 and related proteins, activation of the mitogen activated kinase pathway, activation of cAMP signal transduction pathways, modulation of intracellular calcium homeostasis, and direct antioxidant activity.

REFERENCE COUNT: 151 THERE ARE 151 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 130 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:460461 CAPLUS
DOCUMENT NUMBER: 133:188106
TITLE: Neuroprotection by **estrogens** in a mouse model of focal cerebral ischemia and in cultured neurons: evidence for a receptor-independent antioxidative mechanism
AUTHOR(S): Culmsee, Carsten; Vedder, Helmut; Ravati, Alexander; Junker, Vera; Otto, Dorte; Ahlemeyer, Barbara; Krieg, Jurgen-Christian; Krieglstein, Josef
CORPORATE SOURCE: Institut fur Pharmakologie und Toxikologie, Fachbereich Pharmazie der Philipps-Universitat Marburg, Marburg, D-35032, Germany
SOURCE: Journal of Cerebral Blood Flow and Metabolism (1999), 19(11), 1263-1269
CODEN: JCBMDN; ISSN: 0271-678X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Estrogens** have been suggested for the treatment of neurodegenerative disorders, including stroke, because of their neuroprotective activities against various neurotoxic stimuli such as glutamate, glucose deprivation, iron, or .beta.-**amyloid**. Here, the authors report that 17.beta.-estradiol (0.3 to 30 mg/kg) and 2-OH-estradiol (0.003 to 30 mg/kg) reduced brain tissue damage after permanent occlusion of the middle cerebral artery in male NMRI mice. In vitro, 17.beta.-estradiol (1 to 10 .mu.M) and 2-OH-estradiol (0.01 to 1 .mu.M) reduced the percentage of damaged chick embryonic neurons treated with FeSO4. In these primary neurons exposed to FeSO4, the authors also found reactive oxygen species to be diminished after treatment with 17.beta.-estradiol (1 to 10 .mu.M) or 2-OH-estradiol (0.01 to 10 .mu.M), suggesting a strong antioxidant activity of the **estrogens** that were used. Neither the neuroprotective effect nor the free radical scavenging properties of the **estrogens** were influenced by the **estrogen** receptor antagonist tamoxifen. The authors conclude that **estrogens** protect neurons against damage by radical scavenging rather than through **estrogen** receptor activation.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 131 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:453465 CAPLUS
DOCUMENT NUMBER: 134:3209
TITLE: The role of oxidative stress in the toxicity induced by **amyloid** .beta.-peptide in Alzheimer's disease

AUTHOR(S): Miranda, S.; Opazo, C.; Larrondo, L. F.; Munoz, F. J.; Ruiz, F.; Leighton, F.; Inestrosa, N. C.
CORPORATE SOURCE: P.O. Box 114-D, Facultad de Ciencias Biologicas, Departamento de Biologia Celular y Molecular, Centro de Regulacion Celular y Patologia, Pontificia Universidad Catolica de Chile, Santiago, Chile
SOURCE: Progress in Neurobiology (Oxford) (2000), 62(6), 633-648
CODEN: PGNBA5; ISSN: 0301-0082
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 191 refs. One of the theories involved in the etiol. of Alzheimer's disease (AD) is the oxidative stress hypothesis. The **amyloid** .beta.-peptide (A.beta.), a hallmark in the pathogenesis of AD and the main component of senile plaques, generates free radicals in a metal-catalyzed reaction inducing neuronal cell death by a reactive oxygen species mediated process which damage neuronal membrane lipids, proteins and nucleic acids. Therefore, the interest in the protective role of different antioxidants in AD such as vitamin E, melatonin and **estrogens** is growing. Here, data is reviewed that support the involvement of oxidative stress as an active factor in A.beta.-mediated neuropathol., by triggering or facilitating neurodegeneration, through a wide range of mol. events that disturb neuronal cell homeostasis.
REFERENCE COUNT: 191 THERE ARE 191 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 132 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:366985 CAPLUS
DOCUMENT NUMBER: 133:99758
TITLE: The **estrogen** replacement therapy of the Women's Health Initiative promotes the cellular mechanisms of memory and neuronal survival in neurons vulnerable to Alzheimer's disease
AUTHOR(S): Brinton, Roberta Diaz; Chen, Shuhua; Montoya, Marissa; Hsieh, Debra; Minaya, Jasmin
CORPORATE SOURCE: Department of Molecular Pharmacology and Toxicology and the Program in Neuroscience, Pharmaceutical Sciences Center, USC STAR Program, University of Southern California, Los Angeles, CA, 90033, USA
SOURCE: Maturitas (2000), 34(Suppl. 2), S35-S52
CODEN: MATUDK; ISSN: 0378-5122
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The current study investigated the neurotrophic and neuroprotective action of the complex formulation of conjugated equine **estrogens** (CEEs), the most frequently prescribed **estrogen** replacement therapy in the United States and the **estrogen** replacement therapy of the Women's Health Initiative. Videomicroscopic, morphol. and biochem. analyses were conducted in primary cultures of hippocampal neurons to det. the neurotrophic and neuroprotective properties of CEEs. Results of these analyses demonstrated that CEEs significantly increased hippocampal neuronal outgrowth, a cellular marker of memory formation. Dose response analyses indicated that the lowest effective concn. of CEEs exerted the maximal neurotrophic effect. Of neuroprotection studies demonstrated that CEES induced highly significant neuroprotection against beta amyloid25-35, hydrogen peroxide and glutamate-induced toxicity. CEEs induced cellular markers of memory function in neurons crit. to memory and vulnerable to neg. effects of aging and Alzheimer's disease. In addn., CEEs significantly and potently protected neurons against toxic insults

assocd. with Alzheimer's disease. Because CEEs are the **estrogen** replacement therapy of the Women's Health Initiative, results of the current study could provide cellular mechanisms for effects of CEEs on cognitive function and risk of Alzheimer's disease derived from this prospective clin. trial.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 133 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:354299 CAPLUS
DOCUMENT NUMBER: 133:247078
TITLE: Vascular actions of **estrogen** and Alzheimer's disease
AUTHOR(S): Thomas, T.; Rhodin, J.
CORPORATE SOURCE: Woodlands Medical and Research Center, Oldsmar, FL, 34677, USA
SOURCE: Annals of the New York Academy of Sciences (2000), 903(Vascular Factors in Alzheimer's Disease, 2000), 501-509
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Women are two to three times more likely to develop late-onset Alzheimer's disease (AD) than age-matched men. A large no. of observational reports and a few randomized clin. trials have indicated that **estrogen** replacement therapy (ERT) may retard the development and severity of dementia in postmenopausal women. A chronic inflammatory reaction mediated by abnormal deposition of proteins such as **amyloid** -.beta. (A.beta.) is central to the pathol. of AD. We investigated the effect of low doses of conjugated **estrogen** (Premarin) in an animal model of A.beta.-induced vascular disruption and inflammatory reaction. **Estrogen** prevented vascular deposition of A.beta., endothelial and vessel wall disruption with plasma leakage, platelet and mast cell activation, and characteristic features of an inflammatory reaction: adhesion and transmigration of leukocytes. The beneficial effect was lost when **estrogen** treatment was discontinued. This novel protective effect of **estrogen** against A.beta.-induced vascular dysfunction may contribute to the therapeutic efficacy of **estrogen** in AD and coronary vascular disease.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 134 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:354287 CAPLUS
DOCUMENT NUMBER: 133:265108
TITLE: Animal model of Alzheimer-like vascular pathology and inflammatory reaction
AUTHOR(S): Rhodin, J.; Thomas, T.; Bryant, M.; Sutton, E. T.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, 33612, USA
SOURCE: Annals of the New York Academy of Sciences (2000), 903(Vascular Factors in Alzheimer's Disease, 2000), 345-352
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Blood flow and interaction between formed element and the vascular wall were obsd. with a transparent, thin mesenteric membrane of rodents contg. a 2-dimensional network of microvessels. This in vivo animal model of vascular inflammatory reaction facilitates morphol. and hemodynamic

analyses of leukocyte-endothelial interaction and can be monitored by video microscopy and electron microscopy. The model has served as a rapid means to explore the deleterious vascular actions and inflammatory response to the cytokines tumor necrosis factor, interleukin-1 and **amyloid**-.beta., as well as the protective effects of superoxide dismutase, **estrogen**, and cytokine antagonists.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 135 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:304883 CAPLUS
DOCUMENT NUMBER: 133:53057
TITLE: Development of anti-dementia drugs: Present and future
AUTHOR(S): Nabeshima, Toshitaka; Yamada, Kiyofumi; Noda, Yukihiro; Hasegawa, Masaya; Muraoka, Isao
CORPORATE SOURCE: Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Showa-ku. Nagoya, 466-8560, Japan
SOURCE: Oyo Yakuri (2000), 59(1), 1-9
CODEN: OYYAA2; ISSN: 0300-8533
PUBLISHER: Oyo Yakuri Kenkyukai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review with 44 refs. Senile dementia consists of cerebral vascular dementia and Alzheimer-type dementia. We review pharmacotherapy for senile dementia in the present and development of anti-dementia drugs in the present and future. No. of patients of cerebral vascular dementia is gradually decreased by control the risk factors such as hypertension, hyperlipemia, arteriosclerosis, diabetes. In the present we have only 3 anti-dementia drugs for Alzheimer-type dementia. All of them are cholinesterase inhibitors which prevent dysfunction of cholinergic neuronal system in Alzheimer-type dementia. Other cholinergic agonists and the drugs to non-cholinergic neuronal systems are under the clin. investigations. In future there are many possibilities to develop new drugs to related hypothesis of Alzheimer-type dementia such as inflammation, deficiency of **estrogen**, oxidative stress, .beta.-**amyloid** toxicity, phosphorylation of tau protein, deficiency of neurotrophic factors etc.

L1 ANSWER 136 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:268971 CAPLUS
DOCUMENT NUMBER: 133:895
TITLE: Role of **estrogens** in dementing illnesses: hypotheses on the biological rationale
AUTHOR(S): Govoni, Stefano; Solano, Daniela; Solerte, Bruno S.; Guaita, Antonio; Racchi, Marco
CORPORATE SOURCE: Institute of Pharmacology, University of Pavia, Pavia, 27100, Italy
SOURCE: Medical Science Symposia Series (1999), 13(Women's Health and Menopause), 151-156
CODEN: MSSYEI; ISSN: 0928-9550
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 19 refs., describing neurotrophic and neuroprotective actions of **estrogens**, **estrogens** and **amyloid** precursor protein metab., **estrogens** and genes assocd. with increased risk for Alzheimer's disease (AD), and **estrogens** and Glc utilization. **Estrogen** replacement therapy in the prevention and treatment of AD is discussed.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 137 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:262320 CAPLUS
DOCUMENT NUMBER: 133:38411
TITLE: Effect of Estradiol on Neuronal Swedish-Mutated .beta.-**Amyloid** Precursor Protein Metabolism: Reversal by Astrocytic Cells
AUTHOR(S): Vincent, Bruno; Smith, Jonathan D.
CORPORATE SOURCE: Laboratory of Biochemical Genetics and Metabolism, Rockefeller University, New York, NY, 10021, USA
SOURCE: Biochemical and Biophysical Research Communications (2000), 271(1), 82-85
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease is the most frequent neurodegenerative disorder in the aged population and is characterized by the deposition of the 40/42-residue **amyloid** .beta. protein (A.beta.), a proteolytic fragment of the .beta.-**amyloid** precursor protein (APP). Recently, it has been shown that physiol. doses of estradiol reduce the generation of endogenous A.beta. in primary cortical neurons. Here we investigate the influence of **estrogen** in amyloidogenesis and sAPP.alpha. secretion in the CNS. By means of primary cortical neurons overexpressing humanized APP695 bearing the Swedish mutation (hAPP695sw), we analyzed APP maturation in the absence or in the presence of **estrogen**. We show that **estrogen** at a 2 .mu.M concn. increases the release of the neuroprotective sAPP.alpha. fragment but does not reduce the release of A.beta. in primary neurons overexpressing the Swedish-mutated form of APP. Furthermore, neurons cocultured with astrocytic cells or grown with astrocytes conditioned media do not exhibit the **estrogen**-induced increase in sAPP.alpha. secretion. Altogether, our data indicate that astrocytes interfere with **estrogen** in the regulation of sAPP.alpha. secretion, probably via secreted factor(s). (c) 2000 Academic Press.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 138 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:251153 CAPLUS
DOCUMENT NUMBER: 132:343437
TITLE: Oestrogen and nerve growth factor - neuroprotection and repair in Alzheimer's disease
AUTHOR(S): Granholm, Ann-Charlotte
CORPORATE SOURCE: Departments of Basic Science and Pharmacology and the Neuroscience Training Program, University of Colorado Health Sciences Center, Denver, CO, USA
SOURCE: Expert Opinion on Investigational Drugs (2000), 9(4), 685-694
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 67 refs. The neurogenetics and neuropathol. of Alzheimer's disease (AD) are still largely unknown, even though recent work has clarified some genetic components in this common and devastating neurodegenerative disease. Most of the genetic mutations have been shown to be, at least in the early onset type of AD, related to the function of a large transmembrane protein, **amyloid** precursor protein (APP). This protein is cleaved into various smaller fragments that are either sol. or aggregating. It is thought that this processing of APP is inherently important for the initiation and progression of AD. Recent

animal models have suggested that it is not the formation of .beta.-**amyloid** plaques per se, but the altered processing of APP and the subsequent loss of sol. APP, that sets the stage for the massive neuronal cell loss which occurs in AD. The authors would like to propose a three-way relationship between **estrogen**, APP and nerve growth factor (NGF) in the neural pathways of the brain which are involved in learning and memory - the limbic system. The degeneration of the cholinergic innervation from the basal forebrain to the hippocampal formation in the temporal lobe is thought to be one of the factors detg. the progression of memory decay, both during normal aging and AD. **Estrogen** and NGF are among the neuroprotective agents that have shown some potential for the treatment of AD. Previous results of treatment with these two agents and their relationship to the **amyloid** proteins, will be discussed in this review.

REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 139 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:243638 CAPLUS
DOCUMENT NUMBER: 133:16006
TITLE: Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty
AUTHOR(S): Ershler, William B.; Keller, Evan T.
CORPORATE SOURCE: The Institute for the Advanced Studies in Aging and Geriatric Medicine, Washington, DC, 20006, USA
SOURCE: Annual Review of Medicine (2000), 51, 245-270
CODEN: ARMCAH; ISSN: 0066-4219
PUBLISHER: Annual Reviews Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 197 refs. Interleukin-6 (IL-6) is a proinflammatory cytokine that is normally tightly regulated and expressed at low levels, except during infection, trauma, or other stress. Among several factors that down-regulate IL-6 gene expression are **estrogen** and testosterone. After menopause or andropause, IL-6 levels are elevated, even in the absence of infection, trauma, or stress. IL-6 is a potent mediator of inflammatory processes, and it has been proposed that the age-assocd. increase in IL-6 accounts for certain of the phenotypic changes of advanced age, particularly those that resemble chronic inflammatory disease [decreased lean body mass, osteopenia, low-grade anemia, decreased serum albumin and cholesterol, and increased inflammatory proteins such as C-reactive protein (CRP) and serum **amyloid** A]. Furthermore, the age-assocd. rise in IL-6 has been linked to lymphoproliferative disorders, multiple myeloma, osteoporosis, and Alzheimer's disease. This overview discusses the data relating IL-6 to age-assocd. diseases and to frailty. Like the syndrome of inappropriate antidiuretic hormone, it is possible that certain clin. important late-life changes are due to an inappropriate presence of IL-6.

REFERENCE COUNT: 195 THERE ARE 195 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 140 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:139464 CAPLUS
DOCUMENT NUMBER: 133:72016
TITLE: **Estrogen** and Alzheimer's disease
AUTHOR(S): Nie, Wei; Zhang, Yongxiang
CORPORATE SOURCE: Institute of Poison and Drugs, Military Academy of Medical Sciences, Beijing, 100850, Peop. Rep. China
SOURCE: Shengli Kexue Jinzhan (2000), 31(1), 65-68
CODEN: SLKHA8; ISSN: 0559-7765
PUBLISHER: Zhongguo Shengli Xuehui

DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review with 10 refs., on: (1) effect of **estrogen** on cholinergic neurons in Alzheimer's disease (AD); (2) effect of **estrogen** on enzymes and neurotransmitters in CNS; (3) effect of **estrogen** on **amyloid** protein; (4) effect of **estrogen** on oxidative stress; and (5) effect of **estrogen** on apoE.

L1 ANSWER 141 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:99359 CAPLUS
DOCUMENT NUMBER: 132:203335
TITLE: Testosterone reduces neuronal secretion of Alzheimer's .beta.-**amyloid** peptides
AUTHOR(S): Gouras, Gunnar K.; Xu, Huaxi; Gross, Rachel S.; Greenfield, Jeffrey P.; Hai, Bing; Wang, Rong; Greengard, Paul
CORPORATE SOURCE: Laboratory of Molecular and Cellular Neuroscience and Fisher Center for Research on Alzheimer's Disease, The Rockefeller University, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(3), 1202-1205
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease (AD) is characterized by the age-related deposition of .beta.-**amyloid** (A.beta.) 40/42 peptide aggregates in vulnerable brain regions. Multiple levels of evidence implicate a central role for A.beta. in the pathophysiol. of AD. A.beta. peptides are generated by the regulated cleavage of an .apprxeq.700-amino acid A.beta. precursor protein (.beta.APP). Full-length .beta.APP can undergo proteolytic cleavage either within the A.beta. domain to generate secreted s.beta.APP.alpha. or at the N- and C-terminal domain(s) of A.beta. to generate amyloidogenic A.beta. peptides. Several epidemiol. studies have reported that **estrogen** replacement therapy protects against the development of AD in postmenopausal women. We previously reported that treating cultured neurons with 17.beta.-estradiol reduced the secretion of A.beta.40/42 peptides, suggesting that **estrogen** replacement therapy may protect women against the development of AD by regulating .beta.APP metab. Increasing evidence indicates that testosterone, esp. bioavailable testosterone, decreases with age in older men and in postmenopausal women. We report here that treatment with testosterone increases the secretion of the nonamyloidogenic APP fragment, s.beta.APP.alpha., and decreases the secretion of A.beta. peptides from N2a cells and rat primary cerebrocortical neurons. These results raise the possibility that testosterone supplementation in elderly men may be protective in the treatment of AD.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 142 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:975 CAPLUS
DOCUMENT NUMBER: 132:146805
TITLE: .beta.-Estradiol attenuate **amyloid** .beta.-peptide toxicity via nicotinic receptors
AUTHOR(S): Svensson, A.-L.; Nordberg, A.
CORPORATE SOURCE: Karolinska Institutet, Department of Clinical Neuroscience, Occupational Therapy and Elderly Care Research, Division of Molecular Neuropharmacology, NEUROTEO, NEUROTEO, Huddinge University Hospital, Huddinge, S-141 86, Swed.

SOURCE: NeuroReport (1999), 10(17), 3485-3489
CODEN: NERPEZ; ISSN: 0959-4965
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A no. of epidemiol. studies suggest that **estrogen** therapy is linked to a reduced risk of developing Alzheimer's disease (AD). The present study was conducted to evaluate the effect of 17.beta.-estradiol on .beta.-**amyloid** (A.beta.)-induced toxicity and was performed in rat pheochromocytoma PC 12 cells by measuring the mitochondrial activity. 17.beta.-Estradiol (10-5, 10-6 and 10-8 M) attenuated A.beta.(25-35)-induced toxicity in PC 12 cells. The neuroprotective effect of 17.beta.-estradiol (10-5 M) was prevented in the presence of the nicotinic antagonists methyllycaconitine (MLA) and mecamylamine, suggesting an interaction probably via the .alpha.7 nicotinic receptor subtype. Chronic treatment with 17.beta.-estradiol (10-10-10-5 M) alone did not change the no. of [3H]epibatidine binding sites in human neuroblastoma SH-SY5Y cells and rat PC 12 cells, but significantly prevented the enhanced [3H]epibatidine binding in nicotine-treated PC 12 cells. This study demonstrates that 17.beta.-estradiol exerts neuroprotective effects which might involve interaction with the .alpha.7 nicotinic receptor subtype.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 143 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:770167 CAPLUS
DOCUMENT NUMBER: 132:216375
TITLE: Drug therapy of Alzheimer's disease
AUTHOR(S): Cheng, Yong; Song, You-Hua; Fu, De-Xing
CORPORATE SOURCE: Beijing Hosp., Beijing, 100730, Peop. Rep. China
SOURCE: Zhongguo Linchuang Yaolixue Zazhi (1999), 15(4), 295-298
CODEN: ZLYZE9; ISSN: 1001-6821
PUBLISHER: Beijing Yike Daxue, Linchuang Yaoli Yanjiuso
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review with 15 refs. Alzheimer's disease (AD) is a pathol. of cerebral gray matter resulting in damage to learning ability and memory. The clin. presentation of AD is progressive dementia. At present, the pathogenesis is still unclear, and there are many hypotheses, such as cholinergic lesions, inflammation, free radical-induced lesions, **estrogen** deficiency, cell apoptosis and neurotoxicity of .beta.-**amyloid** protein. This article reviews drug development and clin. aspects of AD therapy, including cholinesterase inhibitors, selective muscarinic agonists, antioxidants, anti-inflammatory agents, **estrogens**, nerve growth factor, calcium channel blockers, inhibitors of .beta.-**amyloid** protein formation, Chinese herbs, etc. Although the drugs currently used in AD ameliorate the symptoms, they do not prevent or delay the development of AD. Combination therapy involving agents with different modes of action may be a future direction of therapy for AD.

L1 ANSWER 144 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:720608 CAPLUS
DOCUMENT NUMBER: 132:77031
TITLE: Association of the **Estrogen** Receptor .alpha. Gene Polymorphisms with Sporadic Alzheimer's Disease
AUTHOR(S): Brandi, Maria Luisa; Becherini, Lucia; Gennari, Luigi; Racchi, Marco; Bianchetti, Angelo; Nacmias, Benedetta; Sorbi, Sandro; Mecocci, Patrizia; Senin, Umberto; Govoni, Stefano
CORPORATE SOURCE: Department of Clinical Physiopathology, University of

Florence, Florence, Italy
SOURCE: Biochemical and Biophysical Research Communications (1999), 265(2), 335-338
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease (AD) is a multifactorial disorder detd. by the interaction of genetic, metabolic, and environmental factors. In the common late-onset familial and sporadic forms of AD apolipoprotein E type 4 allele (APOE-.epsilon.4) is now widely accepted as a major risk factor. The assocn. of **estrogen** treatment with a redn. in the risk of AD together with the modulation by **estrogen** of the secretory metab. of the **amyloid** precursor protein offers new possibilities for identification of other AD susceptibility genes, as those encoding for the **estrogen** receptors (ERs). A total of 193 patients with sporadic late-onset AD, meeting the NINCDS-ADRDA criteria, and a total of 202 control subjects, age and education matched, were included in this study. PvuII and XbaI ER.alpha. and HhaI APOE gene polymorphisms were evaluated in genomic DNA by Polymerase Chain Reaction (PCR). The frequency of the various ER.alpha. genotypes by the combination of P, p and X, x was calcd. for controls and AD patients stratified based on ApoE typing. When the two ER.alpha. gene polymorphisms were analyzed in combination, 7 genotypes were recognized, with a significantly increased prevalence of PPXX genotype in AD patients compared to controls. Risk of AD increased by a factor of 7.6 (CI [1.10-62.3]) in homozygous APOE-.epsilon.4 individuals with PPXX ER.alpha. genotype. These results are consistent with a segregation of PPXX ER.alpha. genotype with a higher risk of developing late-onset sporadic AD in the Italian population. The ER.alpha. gene appears to interact with the APOE-.epsilon.4 genotype in detg. AD susceptibility. (c) 1999 Academic Press.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 145 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:651315 CAPLUS
DOCUMENT NUMBER: 131:332284
TITLE: Long-term deprivation of **estrogens** by ovariectomy potentiates .beta.-**amyloid** -induced working memory deficits in rats
AUTHOR(S): Yamada, Kiyofumi; Tanaka, Tomoko; Zou, Li-Bo; Senzaki, Kouji; Yano, Kohji; Osada, Takashi; Ana, Olariu; Ren, Xiuhai; Kameyama, Tsutomu; Nabeshima, Toshitaka
CORPORATE SOURCE: Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University School of Medicine, Nagoya, 466-8560, Japan
SOURCE: British Journal of Pharmacology (1999), 128(2), 419-427
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, the authors examd. whether deprivation of **estrogens** by ovariectomy could modify learning and memory deficits caused by a continuous intracerebroventricular (i.c.v.) infusion of **amyloid** .beta.-peptide (A.beta.), the major constituent of senile plaques in AD. Neither long-term (3 mo) nor short-term (1 mo), deprivation of **estrogens** by ovariectomy caused a significant impairment in spatial learning and memory in a water maze and spontaneous alternation behavior in a Y-maze. A continuous i.c.v. infusion of A.beta.-(1-42) caused spatial learning and memory deficits in both ovariectomized and sham-operated rats. The A.beta.-induced working memory

deficits were significantly potentiated in ovariectomized rats compared with sham-operated rats when mnemonic ability was examd. 3 mo after ovariectomy. These results suggest that long-term deprivation of **estrogens** induced by ovariectomy increases susceptibility to memory deficits produced by A.beta.-(1-42) in rats.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 146 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:642963 CAPLUS

DOCUMENT NUMBER: 132:164103

TITLE: Neuroprotective approaches in experimental models of .beta.-**amyloid** neurotoxicity: relevance to Alzheimer's disease

AUTHOR(S): Harkany, Tibor; Hortobagyi, Tibor; Sasvari, Maria; Konya, Csaba; Penke, Botond; Luiten, Paul G. M.; Nyakas, Csaba

CORPORATE SOURCE: Central Research Division of Clinical and Experimental Laboratory Medicine, Haynal Imre University of Health Sciences, Budapest, Hung.

SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (1999), 23(6), 963-1008
CODEN: PNPPD7; ISSN: 0278-5846

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with .apprx.175 refs. .beta.-**Amyloid** peptides (A.beta.s) accumulate abundantly in the Alzheimer's disease (AD) brain in areas subserving information acquisition and processing, and memory formation. A.beta. fragments are produced in a process of abnormal proteolytic cleavage of their precursor, the **amyloid** precursor protein (APP). While conflicting data exist in the literature on the roles of A.beta.s in the brain, and particularly in AD, recent studies have provided firm exptl. evidence for the direct neurotoxic properties of A.beta.. Sequence anal. of A.beta.s revealed a high degree of evolutionary conservation and inter-species homol. of the A.beta. amino acid sequence. In contrast, synthetic A.beta. fragments, even if modified fluorescent or isotope-labeled derivs., are pharmacol. candidates for in vitro and in vivo modeling of their cellular actions. During the past decade, acute injection, prolonged mini-osmotic brain perfusion approaches or A.beta. infusions into the blood circulation were developed in order to investigate the effects of synthetic A.beta.s, whereas transgenic models provided insight into the distinct mol. steps of pathol. APP cleavage. The hippocampus, caudate putamen, amygdala and neocortex all formed primary targets of acute neurotoxicity screening, but functional consequences of A.beta. infusions were primarily demonstrated following either intracerebroventricular or basal forebrain (medial septum or magnocellular basal nucleus (MBN)) infusions of A.beta. fragments. In vivo investigations confirmed that, while the active core of A.beta. is located within the .beta.(25-35) sequence, the flanking peptide regions influence not only the folding properties of the A.beta. fragments, but also their in vivo neurotoxic potentials. It has recently been established that A.beta. administration deranges neuron-glia signaling, affects the glial glutamate uptake and thereby induces noxious glutamatergic stimulation of nerve cells. In fact, a crit. role for N-methyl-D-aspartate (NMDA) receptors was postulated in the neurotoxic processes. Addnl., A.beta.s might become internalized, either after their selective binding to cell-surface receptors or after membrane assocn. in consequence of their highly lipophilic nature, and induce free radical generation and subsequent oxidative injury. Ca2+-mediated neurotoxic events and generation of oxygen free radicals may indeed potentiate each other, or even converge to the same neurotoxic events, leading to cell

death. Neuroprotection against A.beta. toxicity was achieved by both pre- and post-treatment with NMDA receptor channel antagonists. Moreover, direct radical-scavengers, such as vitamin E or vitamin C, attenuated A.beta. toxicity with high efficacy. Interestingly, combined drug treatments did not necessarily result in additive enhanced neuroprotection. Similar to the blockade of NMDA receptors, the neurotoxic action of A.beta.s could be markedly decreased by pharmacol. manipulation of voltage-dependent Ca2+-channels, serotonergic 1A or adenosine A1 receptors, and by drugs eliciting membrane hyperpolarization or indirect blockade of Ca2+-mediated intracellular consequences of intracerebral A.beta. infusions. A.beta. neurotoxicity might be dose-dependently modulated by trace metals. In spite of the fact that zinc (Zn) may act as a potent inhibitor of the NMDA receptor channel, high Zn doses accelerate A.beta. fibril formation, stabilize the .beta.-sheet conformation and thereby potentiate A.beta. neurotoxicity. Combined trace element supplementation with Se, Mn, or Mg, which prevails over the expression of detoxifying enzymes or counteracts intracellular elevations of Ca2+, may reduce the neurotoxic impact of A.beta.s. Alterations in the regulatory functions of the hypothalamo-pituitary-adrenal axis may contribute significantly to neurodegenerative changes in the brain. Furthermore, AD patients exhibit substantially increased circadian levels of steroid hormones, as well as baseline cortisol concns. In fact, a dose-dependent regulatory action of corticosterone on A.beta. or NMDA excitotoxicity has recently been demonstrated on MBN neurons, yielding a reversed bell-shaped dose-response profile. Furthermore, characteristic neuroprotective properties were postulated for **estrogen** both in vitro and in vivo. A novel approach in which ".beta.-sheet breaker" peptide analogs are applied for the elimination of A.beta. fibrillogenesis/aggregation, or for the prevention of the direct binding of A.beta.s to possible selective cell-surface recognition sites (A.beta. receptors) provides promising in vivo tools for the prevention of A.beta. toxicity.

REFERENCE COUNT: 175 THERE ARE 175 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 147 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:637213 CAPLUS

DOCUMENT NUMBER: 131:332272

TITLE: Sodium salicylate and 17.beta.-estradiol attenuate nuclear transcription factor NF-.kappa.B translocation in cultured rat astroglial cultures following exposure to **amyloid** A.beta.1-40 and lipopolysaccharides

AUTHOR(S): Dodel, Richard C.; Du, Yansheng; Bales, Kelly R.; Gao, Feng; Paul, Steven M.

CORPORATE SOURCE: Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, IN, 46202, USA

SOURCE: Journal of Neurochemistry (1999), 73(4), 1453-1460
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In recent years inflammatory mechanisms have become increasingly appreciated as important steps in the Alzheimer's pathogenic pathway. There is accumulating evidence that **amyloid** .beta.-peptide (A.beta.), the peptide product of the cleavage of **amyloid** precursor protein, may promote or exacerbate local inflammation by stimulating glial cells to release immune mediators. In addn., clin. studies using nonsteroidal antiinflammatory drugs have found a reduced risk for Alzheimer's disease with their use. Here we show that the

neurotoxic A.beta., a major plaque component, and lipopolysaccharides (LPS), an immune reaction-triggering portion of bacterial membranes, are both potent activators of the nuclear transcription factor NF-.kappa.B in primary rat astroglial cells. The activation was found to be concn.- and time-dependent and could be attenuated in the presence of NF-.kappa.B decoy nucleotides. The pretreatment by either 17.beta.-estradiol (1-10 .mu.g) or sodium salicylate (3-30 mM) reduced the A.beta. (LPS)-induced activation of NF-.kappa.B by 48 (50%) and 60% (50%) of activated levels, resp. In addn., 17.beta.-estradiol (10 .mu.M) and sodium salicylate (10 mM) were able to attenuate the increase in interleukin-1.beta. levels following exposure to 25 .mu.M A.beta.. Our data suggest that the aberrant gene expression is at least in part due to A.beta.-induced activation of NF-.kappa.B, a potent immediate-early transcriptional regulator of numerous proinflammatory genes; this event takes place in astroglial cells. The results of our expts. provide a further understanding of the effects of **estrogen** and aspirin on astroglial cells exposed to A.beta. and LPS.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 148 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:626037 CAPLUS
DOCUMENT NUMBER: 131:252579
TITLE: Hypocholesteremics for decreasing beta **amyloid** protein and prevention of Alzheimer's disease
INVENTOR(S): Yankner, Bruce A.; Nadeau, Philip
PATENT ASSIGNEE(S): Children's Medical Center Corporation, USA
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9948488 | A2 | 19990930 | WO 1999-US6396 | 19990323 |
| WO 9948488 | A3 | 20000622 | | |
| W: AU, CA, JP | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| US 6080778 | A | 20000627 | US 1998-46235 | 19980323 |
| CA 2324999 | AA | 19990930 | CA 1999-2324999 | 19990323 |
| AU 9932009 | A1 | 19991018 | AU 1999-32009 | 19990323 |
| AU 759257 | B2 | 20030410 | | |
| EP 1063980 | A2 | 20010103 | EP 1999-914084 | 19990323 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002507564 | T2 | 20020312 | JP 2000-537538 | 19990323 |

PRIORITY APPLN. INFO.: US 1998-46235 A 19980323
WO 1999-US6396 W 19990323

AB Blood cholesterol levels are correlated with prodn. of **amyloid** .beta. protein ((A).beta.), and are predictors of populations at risk of developing Alzheimer's disease (AD). Methods for lowering blood cholesterol levels can be used to decrease prodn. of A.beta., thereby decreasing the risk of developing AD. The same methods and compns. can also be used for treating individuals diagnosed with AD. Methods include administration of compds. which increase uptake of cholesterol by the liver, such as the administration of HMG CoA reductase inhibitors, administration of compds. which block endogenous cholesterol prodn., such as the administration of HMG CoA reductase inhibitors, administration of compns. which prevent uptake of dietary cholesterol, and administration of

combinations of any of these which are effective to lower blood cholesterol levels. Methods have also been developed to predict populations at risk, based on the role of cholesterol in prodn. of A.beta.. For example, individuals with Apo E4 and high cholesterol, defined as a blood cholesterol level of greater than 200 mg/dL, post menopausal women with high cholesterol levels - esp. those who are not taking **estrogen**, or individuals with high blood cholesterol levels who are not obese are all at risk of developing AD if blood cholesterol levels are not decreased.

L1 ANSWER 149 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:615343 CAPLUS
DOCUMENT NUMBER: 131:309317
TITLE: Neurohormonal signaling pathways and the regulation of Alzheimer .beta.-**amyloid** precursor metabolism
AUTHOR(S): Gandy, Sam
CORPORATE SOURCE: Department of Psychiatry, The Nathan S. Kline Institute Psychiatric Research, New York University, Orangeburg, NY, 10962, USA
SOURCE: Trends in Endocrinology and Metabolism (1999), 10(7), 273-279
CODEN: TENME4; ISSN: 1043-2760
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 50 refs. Postmenopausal women on **estrogen** replacement appear to have their relative risk of developing Alzheimer's disease diminished by about one half. Because brain **amyloid** accumulation plays a key role in initiating Alzheimer's pathol., it is attractive to postulate that **estrogen** might modulate Alzheimer's risk by inhibiting **amyloid** accumulation. Data and cell biol. models supporting such a scenario are reviewed here.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 150 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:608153 CAPLUS
DOCUMENT NUMBER: 132:45023
TITLE: Theoretical basis for the benefit of postmenopausal **estrogen** substitution
AUTHOR(S): Miller, M. M.; Franklin, K. B. J.
CORPORATE SOURCE: Royal Victoria Hospital, and Centre for Studies on Aging, Experimental Medicine, Anatomy, Departments of Obstetrics and Gynecology, McGill University, Montreal, QC, Can.
SOURCE: Experimental Gerontology (1999), 34(5), 587-604
CODEN: EXGEAB; ISSN: 0531-5565
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with .apprx.75 refs. Women are being presented with an increasing no. of choices for health care management as they move through the aging process. **Estrogen** has pos. effects on mood, sexual function, target end organs and cognitive function, and may play an important role in the etiol. of Alzheimer's Disease by acting to prevent **amyloid** plaque formation, oxidative stress, or deterioration of the cholinergic neurotransmitter system. The benefits of **estrogen** therapy for osteoporosis, the cardiovascular system, and lipid metab. are far reaching, but the possibility of developing breast cancer later in life is also relevant. Understanding the mechanisms for the action of the **estrogens**, anti-**estrogens**, and the selective

**estrogen** receptor modulators, and possible alternative routes of symptom management for some menopausal events is important to make appropriate decisions on choice of therapy. This review discusses the theor. basis for **estrogen**'s actions in the management of the postmenopausal stage of the life cycle.

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 151 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:561955 CAPLUS
DOCUMENT NUMBER: 131:197733
TITLE: Mitochondrial genome lesions in the pathogenesis of sporadic Alzheimer's disease
AUTHOR(S): Meier-Ruge, W. A.; Bertoni-Freddari, C.
CORPORATE SOURCE: Div. Gerontological Brain Research, Dep. Pathology, Medical School, Univ. Basel, Basel, CH-4003, Switz.
SOURCE: Gerontology (Basel) (1999), 45(5), 289-297
CODEN: GERNDJ; ISSN: 0304-324X
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 96 refs., describing mitochondrial energy defects, ATP prodn. and apoptosis, Alzheimer's disease (AD), Glc turnover and mitochondrial performance, ATP and .beta.-**amyloid** precursor protein processing, and strategies of exptl. pharmacol. in AD. Peroxidative alterations in mitochondrial DNA are of importance in degenerative diseases of postmitotic tissues, particularly in degenerative diseases, offering a new pharmacol. approach for the treatment of AD. Neurothrophic factors and **estrogen** are supposed to be the first pharmacol. leads.

REFERENCE COUNT: 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 152 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:488306 CAPLUS
DOCUMENT NUMBER: 131:139695
TITLE: Improvement in functions of the central nervous system by **estrogen** replacement therapy might be related with an increased nitric oxide production
AUTHOR(S): Lopez-Jaramillo, Patricio; Teran, Enrique
CORPORATE SOURCE: Mineral Metabolism Unit, Fac. Medicine, Central Univ. Ecuador, Quito, Ecuador
SOURCE: Endothelium (1999), 6(4), 263-266
CODEN: ENDTE9; ISSN: 1062-3329
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Estrogen** promotes neurons growth, prevents neuronal cell atrophy, and regulates synaptic plasticity. A administration of **estrogen** protects neurons against oxidative stress, excitotoxins, and .beta.-**amyloid**-induced toxicity in cell culture. It was shown that **estrogen** treatment reduces the blood serum monoamino oxidase levels and might regulate learning and memory. Nitric oxide (NO) is a retrograde messenger and long-term potentiation can be block using NO-synthase inhibitors or can be prevent with NO-scavengers. NO synthase is widespread in the central nervous system and acts as neurotransmitter/neuromodulator. The actions of serotonine, bradykinin, endothelin, acetylcholine, and noradrenaline might be linked to NO formation. **Estrogen** induces activity of constitutive NO synthase and **estrogen** replacement therapy in postmenopausal women increases circulating nitrite plus nitrate levels. The effect of **estrogen** on NO synthesis is rapid and is maintained with repeated

administration. The effects of **estrogen** replacement therapy demonstrated in Andean postmenopausal women were assocd. with a increase in plasma levels of nitrite plus nitrate. The authors hypothesis is that beneficial effect of **estrogen** replacement therapy on involutive depression in postmenopausal women is mediated by increase in NO prodn. by central nervous system.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 153 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:469986 CAPLUS
DOCUMENT NUMBER: 131:242493
TITLE: Phytoestrogen kaempferol (3,4',5,7-tetrahydroxyflavone) protects PC12 and T47D cells from .beta.-**amyloid**-induced toxicity
AUTHOR(S): Roth, Adrian; Schaffner, Willy; Hertel, Cornelia
CORPORATE SOURCE: Pharma Research Preclinical, F. Hoffmann-LaRoche Ltd, Basel, 4070, Switz.
SOURCE: Journal of Neuroscience Research (1999), 57(3), 399-404
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In clin. studies, it has been shown that **estrogen** replacement therapy in menopause is strongly correlated with a reduced risk of the development of Alzheimer's disease (AD). In in vitro expts., it was demonstrated that estradiol protects cells against the toxic effects of .beta.-**amyloid**, the major component of plaques in brains of AD patients. Therefore, **estrogens** have become interesting candidates for a possible treatment of neurodegeneration. In plants, a class of compds. has been identified that bind to human **estrogen** receptor, so-called phytoestrogens, which are part of our daily diet. Here, we compared the effects of .alpha.- and .beta.-estradiol with plant-derived kaempferol on .beta.-**amyloid** peptide-induced toxicity in PC12 neuroblastoma and T47D human breast cancer cells. The present results demonstrate a protective effect of kaempferol comparable to that obsd. with estradiol. The effects of the weak **estrogen** receptor agonists .alpha.-estradiol and kaempferol were found to be similar to the effects of the strong **estrogen** receptor agonist .beta.-estradiol, suggesting a mode of action independent from the nuclear **estrogen** receptor.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 154 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:466945 CAPLUS
DOCUMENT NUMBER: 131:239602
TITLE: Human brain short chain L-3-hydroxyacyl coenzyme A dehydrogenase is a single-domain multifunctional enzyme. Characterization of a novel 17.beta.-hydroxysteroid dehydrogenase
AUTHOR(S): He, Xue-Ying; Merz, George; Mehta, Pankaj; Schulz, Horst; Yang, Song-Yu
CORPORATE SOURCE: Department of Pharmacology, New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY, 10314, USA
SOURCE: Journal of Biological Chemistry (1999), 274(21), 15014-15019
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human brain short chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD) was found to catalyze the oxidn. of 17.beta.-estradiol and dihydroandrosterone as well as alcs. Mitochondria have been demonstrated to be the proper location of this NAD+-dependent dehydrogenase in cells, although its primary structure is identical to an **amyloid** .beta.-peptide binding protein reportedly assocd. with the endoplasmic reticulum (ERAB). This fatty acid .beta.-oxidn. enzyme was identified as a novel 17.beta.-hydroxysteroid dehydrogenase responsible for the inactivation of sex steroid hormones. The catalytic rate const. of the purified enzyme was estd. to be 0.66 min-1 with apparent Km values of 43 and 50 .mu.M for 17.beta.-estradiol and NAD+, resp. The catalytic efficiency of this enzyme for the oxidn. of 17.beta.-estradiol was comparable with that of peroxisomal 17.beta.-hydroxysteroid dehydrogenase type 4. As a result, the human SCHAD gene product, a single-domain multifunctional enzyme, appears to function in two different pathways of lipid metab. Because the catalytic functions of human brain short chain L-3-hydroxyacyl-CoA dehydrogenase could weaken the protective effects of **estrogen** and generate aldehydes in neurons, it is proposed that a high concn. of this enzyme in brain is a potential risk factor for Alzheimer's disease.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 155 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:419531 CAPLUS
DOCUMENT NUMBER: 131:67568
TITLE: Vitamin E and other antioxidants in neuroprotection
AUTHOR(S): Behl, Christian
CORPORATE SOURCE: Neurodegeneration Group, Max-Planck-Institute Psychiatry, Munich, D-80804, Germany
SOURCE: International Journal for Vitamin and Nutrition Research (1999), 69(3), 213-219
CODEN: IJVNAP; ISSN: 0300-9831
PUBLISHER: Hogrefe & Huber Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 49 refs. is given. Several pathol. conditions are believed to be causally related to the generation of reactive oxygen species and free radicals including various neurodegenerative disorders. In the histopathol. of Alzheimer's disease (AD) many signs of oxidative reactions can be found building the basis of the oxidative stress hypothesis of AD. One major player in the generation of an overall oxidative microenvironment for the nerve cells is the **amyloid** .beta. protein (A.beta.) of the senile plaques in brain areas affected in AD. A.beta. can be neurotoxic and this toxicity is mediated by peroxides and by the peroxidn. of membrane lipids leading to the lysis of the cell, Consequently, lipophilic free radical scavengers such as vitamin E and the recently discovered antioxidant activity of the female sex hormone **estrogen** protects neurons against the oxidative toxicity of A.beta. and other AD-related oxidative insults. In a first clin. trial using vitamin E in therapy, this antioxidant could slow down the course of the disease launching further clin. investigations. Although antioxidants act as non-specific protective chem. shields for neurons and do not target specific pathol. events, they are highly effective and further investigations on their activity might lead to an even more effective application of antioxidants. Since the knowledge of the pathways of neuronal cell death that occur during oxidative challenges is increasing, it will he of central interest how antioxidants can interfere with signal transduction mechanisms and therefore also modify genetic programs. As long as specific interventions are not available the optimistic data concerning the neuroprotective activity of antioxidants in vitro and in

vivo underline an important role for antioxidative acting compds. for the prevention and therapy of oxidative stress-related conditions including AD.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 156 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:338775 CAPLUS
DOCUMENT NUMBER: 131:86
TITLE: Recent developments in the drug treatment of Alzheimer's disease
AUTHOR(S): Sramek, John J.; Cutler, Neal R.
CORPORATE SOURCE: California Clinical Trials, Beverly Hills, CA, USA
SOURCE: Drugs & Aging (1999), 14(5), 359-373
CODEN: DRAGE6; ISSN: 1170-229X
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 150 refs. Alzheimer's disease (AD) is a chronic neurodegenerative disorder with an impact on public health which continues to increase with the increasing longevity of the population. The disease is characterized clin. by a progressive loss of cognitive and behavioral function. These deficits are thought to result from decreased cholinergic transmission; therefore, restoring cholinergic function has been the main focus in the development of drugs for AD. Several pharmacol. approaches to enhancing cholinergic function have been developed for symptomatic or palliative therapy of AD. Although these strategies have resulted in modest cognitive and behavioral improvements in patients with AD, they do not address the underlying progression of the disease. New strategies will be required to slow, stop or reverse the effects of neuro-degeneration in AD. A no. of potential therapies are currently under investigation, including **estrogen** replacement, anti-inflammatory agents, free radical scavengers and antioxidants, and monoamine oxidase-B (MAO-B) inhibitors. The evidence for a protective effect of **estrogens** or nonsteroidal anti-inflammatory drugs (NSAIDs) is controversial, and largely based on retrospective studies. More controlled prospective studies are needed to definitively demonstrate the benefits of long term **estrogen** or NSAID use in the prevention of AD. Free radical scavengers/antioxidants such as idebenone, and selective prevention MAO-B inhibitors such as lazabemide are well tolerated, but require addnl. studies in order to demonstrate preventative effects. In addn., other approaches, such as anti-**amyloid** treatments that affect beta-amylase secretion, aggregation and toxicity, appear promising; treatments that hinder neurofibrillary tangle construction and nerve growth factor (NGF) induction are in the very early stages of development.

REFERENCE COUNT: 150 THERE ARE 150 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 157 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:335106 CAPLUS
DOCUMENT NUMBER: 131:110769
TITLE: Perspectives of pharmacotherapy in Alzheimer's disease
AUTHOR(S): Yamada, Kiyofumi; Ren, Xiuhai; Nabeshima, Toshitaka
CORPORATE SOURCE: Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University School of Medicine, Nagoya, 466-8560, Japan
SOURCE: Japanese Journal of Pharmacology (1999), 80(1), 9-14
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 30 refs. Alzheimer's disease (AD) is the most common cause of progressive decline of cognitive function in aged humans, and it is characterized by the presence of numerous senile plaques and neurofibrillary tangles accompanied by neuronal loss. The senile plaques are composed of **amyloid** .beta.-peptides (A.beta.), 40-42 amino acid peptide fragments of the .beta.-**amyloid** precursor protein. Genetic, mol. biol. and neuropharmacol. evidence support the " **amyloid** cascade hypothesis" for the pathogenesis of the disease. We review the in vivo effects of various compds. on behavioral and neuropathol. changes in the non-transgenic animal models of AD produced by continuous i.c.v. infusion of A.beta.. These results support therapeutic strategies such as cholinergic therapy, anti-inflammatory agents, antioxidants and **estrogen** replacement therapy, as well as other cognition enhancers for the treatment of AD. In addn., the **amyloid** cascade hypothesis offers a no. of potential targets for novel therapeutic strategies in AD. We believe that our non-transgenic animal model, as well as transgenic animal models, are useful for developing novel pharmacotherapeutics in AD.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 158 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:222855 CAPLUS
DOCUMENT NUMBER: 130:262134
TITLE: Methods for increasing apoE levels for the treatment of neurodegenerative disease
INVENTOR(S): Poirier, Judes
PATENT ASSIGNEE(S): Nova Molecular, Inc., Can.
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9915159 | A2 | 19990401 | WO 1998-IB1679 | 19980924 |
| WO 9915159 | A3 | 20000217 | | |
| W: AU, CA, FI, JP, MX, NZ, SG | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2304505 | AA | 19990401 | CA 1998-2304505 | 19980924 |
| AU 9894540 | A1 | 19990412 | AU 1998-94540 | 19980924 |
| EP 1017375 | A2 | 20000712 | EP 1998-947709 | 19980924 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| US 6274603 | B1 | 20010814 | US 1998-160462 | 19980924 |
| JP 2001517617 | T2 | 20011009 | JP 2000-512529 | 19980924 |
| US 2001051602 | A1 | 20011213 | US 2001-888245 | 20010622 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1997-59908P | P | 19970924 |
| US 1998-160462 | A1 | 19980924 |
| WO 1998-IB1679 | W | 19980924 |

AB A method is disclosed for reducing neurodegenerative disease in patients by administration of a therapeutically effective amt. of a compd. which can increase ApoE levels. Compds. of the invention include e.g. probucol.

L1 ANSWER 159 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:214728 CAPLUS
DOCUMENT NUMBER: 131:858
TITLE: **Estrogen** modulates neuronal Bcl-XL

expression and .beta.-**amyloid**-induced apoptosis: relevance to Alzheimer's disease

AUTHOR(S): Pike, Christian J.

CORPORATE SOURCE: Institute for Brain Aging and Dementia, Gillespie Neuroscience Research Facility, University of California-Irvine, Irvine, CA, 92697-4540, USA

SOURCE: Journal of Neurochemistry (1999), 72(4), 1552-1563
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recent findings indicate that **estrogen** is neuroprotective, a cellular effect that may contribute to its clin. benefits in delaying the development of Alzheimer's disease. The authors identify a novel neuronal action of **estrogen** that may contribute to its neuroprotective mechanism(s). Specifically, the authors report that **estrogen** significantly increases the expression of the anti-apoptotic protein Bcl-xL in cultured hippocampal neurons. This effect presumably reflects classic **estrogen** transcriptional regulation, as the authors identified a putative **estrogen** response element in the bcl-x gene. **Estrogen**-induced enhancement of Bcl-xL is assocd. with a redn. in measures of .beta.-**amyloid**-induced apoptosis, including inhibition of both caspase-mediated proteolysis and neurotoxicity. A similar relationship between **estrogen**, Bcl-xL expression, and resistance to degeneration was also obsd. in human hippocampus. The authors report neuronal colocalization of **estrogen** receptor and Bcl-xL immunoreactivities that is most prominent in hippocampal subfield CA3, a region that shows relatively little immunoreactivity to paired helical filament-1, a marker of Alzheimer's disease neurodegeneration. These data suggest a novel mechanism of **estrogen** neuroprotection that may be relevant to **estrogen**'s suggested ability to modulate neuronal viability across the life span, from neural sexual differentiation and development through age-related neurodegenerative conditions.

REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 160 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:194338 CAPLUS

DOCUMENT NUMBER: 130:234342

TITLE: Fluorescence polarization method.

INVENTOR(S): Nakayama, Hiroshi; Miyazaki, Jinsei

PATENT ASSIGNEE(S): Matsushita Electric Industrial Co., Ltd., Japan

SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9913332 | A1 | 19990318 | WO 1998-JP3988 | 19980904 |
| W: CA, CN, JP, KR, US | | | | |
| RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 957365 | A1 | 19991117 | EP 1998-941732 | 19980904 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 3255293 | B2 | 20020212 | JP 1999-515341 | 19980904 |
| US 2001051331 | A1 | 20011213 | US 1999-297603 | 19990723 |
| US 6432632 | B2 | 20020813 | | |

US 2002150890 A1 20021017 US 2002-163826 20020605
PRIORITY APPLN. INFO.: JP 1997-240672 A 19970905
WO 1998-JP3988 W 19980904
US 1999-297603 A1 19990723

AB Fluorescence polarization immunoassay is described for analyzing an object in a sample. The first step of this method is to provide a fluorescence-labeled protein in which a protein capable of specifically binding to the object and a fluorrescent dye are covalently bound. The second step is to react the fluorescence-labeled protein with the object. The last step is to measure a change in fluorescence polarization of the fluorescence-labeled protein bound to the object. Examples are shown with the detn. of various antigens (e.g. CRP, HDL, LDL, E. coli) using resp. specific antibodies labeled with pyrene deriv.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 161 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:164728 CAPLUS
DOCUMENT NUMBER: 130:262234
TITLE: **Estrogen** replacement therapy and Alzheimer's disease
AUTHOR(S): Nikolov, R.; Kuhl, H.; Golbs, S.
CORPORATE SOURCE: Department of Pharmacology, Chemical Pharmaceutical Research Institute, Sofia, BG-1756, Bulg.
SOURCE: Drugs of Today (1998), 34(11), 927-933
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 45 refs. **Estrogen** replacement therapy (ERT) is increasingly recommended for postmenopausal women due to its numerous beneficial effects on bone, cardiovascular system, brain function and quality of life. Data from retrospective epidemiol. studies have shown that ERT has a potential to reduce the risk for developing Alzheimer's disease (AD) and to delay its progression. In addn., recent clin. studies have reported improvement of cognitive functions in women with AD. Findings from basic science indicated that the possible mechanisms of action by which **estrogen** may affect AD include interaction with cholinergic neurotransmitter system, cholinergic neurotropic and neuroprotective effect, improvement of learning and memory, improvement of cerebral blood flow and metab., antioxidant and antiinflammatory action, and interference with .beta.-**amyloid** protein metab. and toxicity. **Estrogen** use in post-menopausal women may offer a new approach for improving cognitive functions in nondemented and demented women, delaying the onset and progression of AD and reducing its occurrence. However, prospective clin. trials are required to establish the efficacy of ERT for prevention and treatment of AD.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 162 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:133150 CAPLUS
DOCUMENT NUMBER: 130:336065
TITLE: Vascular nitric oxide may lessen Alzheimer's risk
AUTHOR(S): McCarty, M. F.
CORPORATE SOURCE: Nutrition 21, San Diego, CA, 92109, USA
SOURCE: Medical Hypotheses (1998), 51(6), 465-476
CODEN: MEHYDY; ISSN: 0306-9877
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 173 refs. **Estrogen** deficiency, hyperinsulinemia,

type II diabetes, atherosclerosis, and a past history of elevated blood pressure may be assocd. with increased risk of Alzheimer's disease (AD). Common to all of these risk factors is a diminished capacity of vascular endothelium to generate nitric oxide (NO). Vascular NO has the potential to enhance the membrane polarization of cerebral neurons by increasing the open probability of calcium-activated potassium channels; this may protect neurons from the excessive calcium influx, potentiated by .beta.-**amyloid** peptides that is thought to mediate neuronal damage in AD. The possibility that NO/cGMP may modulate the synthesis or processing of the **amyloid** precursor protein, also merits evaluation. Practical measures for promoting vascular NO prodn. may include increased intakes of arginine, potassium, antioxidants, and fish-oil, as well as lifestyle measures that typically lower elevated blood pressure; potential benefits of chromium, glucosamine, and silicon should also be explored. In hypertensives, angiotensin-converting enzyme (ACE) inhibitors and sodium restriction may favorably influence endothelial function. Fish-oil should have the addnl. benefit of antagonizing the contribution of interleukin-1 to AD pathogenesis. Ancillary anti-excitotoxic measures such as magnesium, taurine, phenytoin, and vasodilators targeting ATP-dependent potassium (KATP) channels, may likewise reduce AD risk. Most of the nutritional measures suggested here would in any case be recommendable for preservation of vascular health.

REFERENCE COUNT: 173 THERE ARE 173 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 163 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:71692 CAPLUS

DOCUMENT NUMBER: 130:261592

TITLE: A novel synthetic oleanane triterpenoid, 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, with potent differentiating, antiproliferative, and anti-inflammatory activity

AUTHOR(S): Suh, Nanjoo; Wang, Yongping; Honda, Tadashi; Gribble, Gordon W.; Dmitrovsky, Ethan; Hickey, William F.; Maue, Robert A.; Place, Andrew E.; Porter, Donna M.; Spinella, Michael J.; Williams, Charlotte R.; Wu, Gengfei; Dannenberg, Andrew J.; Flanders, Kathleen C.; Letterio, John J.; Mangelsdorf, David J.; Nathan, Carl F.; Nguyen, Lananh; Porter, Weston W.; Ren, Renee F.; Roberts, Anita B.; Roche, Nanette S.; Subbaramaiah, Kotha; Sporn, Michael B.

CORPORATE SOURCE: Norris Cotton Cancer Center, Department of Pharmacology, Dartmouth Medical School, Hanover, NH, 03755, USA

SOURCE: Cancer Research (1999), 59(2), 336-341
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The new synthetic oleanane triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) is a potent, multifunctional mol. It induces monocytic differentiation of human myeloid leukemia cells and adipogenic differentiation of mouse 3T3-L1 fibroblasts and enhances the neuronal differentiation of rat PC12 pheochromocytoma cells caused by nerve growth factor. CDDO inhibits proliferation of many human tumor cell lines, including those derived from **estrogen** receptor-pos. and -neg. breast carcinomas, myeloid leukemias, and several carcinomas bearing a Smad4 mutation. Furthermore, it suppresses the abilities of various inflammatory cytokines, such as IFN-.gamma., interleukin-1, and tumor necrosis factor-.alpha., to induce de novo formation of the enzymes inducible nitric oxide synthase (iNos) and inducible cyclooxygenase

(COX-2) in mouse peritoneal macrophages, rat brain microglia, and human colon fibroblasts. CDDO will also protect rat brain hippocampal neurons from cell death induced by .beta.-**amyloid**. The above activities have been found at concns. ranging from 10-6 to 10-9 M in cell culture, and these results suggest that CDDO needs further study in vivo, for either chemoprevention or chemotherapy of malignancy as well as for neuroprotection.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 164 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:55994 CAPLUS
DOCUMENT NUMBER: 130:265542
TITLE: Cellular and molecular basis of **estrogen**'s neuroprotection: potential relevance for Alzheimer's disease
AUTHOR(S): Inestrosa, Nibaldo C.; Marzolo, Maria-Paz; Bonnefont, Andrea B.
CORPORATE SOURCE: Departamento de Biologia Celular y Molecular, Facultad de Ciencias, Pontificia Universidad Catolica de Chile, Chile
SOURCE: Molecular Neurobiology (1998), 17(1-3), 73-86
CODEN: MONBEW; ISSN: 0893-7648
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 124 refs. Alzheimer's disease (AD) is one of the most common types of dementia among the aged population, with a higher prevalence in women. The reason for this latter observation remained unsolved for years, but recent studies have provided evidence that a lack of circulating **estrogen** in postmenopausal women could be a relevant factor. Moreover, follow-up studies among postmenopausal women who had received **estrogen**-replacement therapy (ERT), suggested that they had a markedly reduced risk of developing AD. In addn., studies among older women who already had AD indeed confirmed that a decrease in **estrogen** levels was likely to be an important factor in triggering the pathogenesis of the disease. In this review article, the authors will discuss the evidence suggesting that **estrogen** may have a protective role against AD, mainly through its action as: a trophic factor for cholinergic neurons, a modulator for the expression of apolipoprotein E (ApoE) in the brain, an antioxidant compd. decreasing the neuronal damage caused by oxidative stress, and a promoter of the physiol. nonamyloidogenic processing of the **amyloid** precursor protein (APP), decreasing the prodn. of the **amyloid**-.beta.-peptide (A.beta.), a key factor in the pathogenesis of AD.

REFERENCE COUNT: 124 THERE ARE 124 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 165 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:47867 CAPLUS
DOCUMENT NUMBER: 130:250245
TITLE: Alzheimer's disease and oxidative stress: Implications for novel therapeutic approaches
AUTHOR(S): Behl, Christian
CORPORATE SOURCE: Max Planck Institute of Psychiatry, Munich, 80804, Germany
SOURCE: Progress in Neurobiology (Oxford) (1998), Volume Date 1999, 57(3), 301-323
CODEN: PGNBA5; ISSN: 0301-0082
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 293 refs. Alzheimer's disease (AD) is a progressive neurodegenerative disorder with a deadly outcome. AD is the leading cause of senile dementia and although the pathogenesis of this disorder is not known, various hypotheses have been developed based on exptl. data accumulated since the initial description of this disease by Alois Alzheimer about 90 yr ago. Most approaches to explain the pathogenesis of AD focus on its two histopathol. hallmarks, the **amyloid** .beta. protein- (A.beta.-) loaded senile plaques and the neurofibrillary tangles, which consist of the filament protein tau. Various lines of genetic evidence support a central role of A.beta. in the pathogenesis of AD and an increasing no. of studies show that oxidn. reactions occur in AD and that A.beta. may be one mol. link between oxidative stress and AD-assocd. neuronal cell death. A.beta. itself can be neurotoxic and can induce oxidative stress in cultivated neurons. A.beta. is, therefore, one player in the concert of oxidative reactions that challenge neurons besides inflammatory reactions which are also assocd. with the AD pathol. Consequently, antioxidant approaches for the prevention and therapy of AD are of central interest. Exptl. as well as clin. data show that lipophilic antioxidants, such as vitamin E and **estrogens**, are neuroprotective and may help patients suffering from AD. While an addnl. intensive elucidation of the cellular and mol. events of neuronal cell death in AD will, ultimately, lead to novel drug targets, various. antioxidants are already available for a further exploitation of their preventive and therapeutic potential.

REFERENCE COUNT: 293 THERE ARE 293 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 166 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:815236 CAPLUS
DOCUMENT NUMBER: 130:250179
TITLE: Mechanisms of pathogenesis of Alzheimer's disease
AUTHOR(S): Li, Lin
CORPORATE SOURCE: Department of neurobiology, Shanxi Medical University, Taiyuan, 030001, Peop. Rep. China
SOURCE: Shengli Kexue Jinzhan (1998), 29(4), 344-348
CODEN: SLKHA8; ISSN: 0559-7765
PUBLISHER: Zhongguo Shengli Xuehui
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese

AB A review with 10 refs. on mechanism of pathogenesis of Alzheimer's disease (AD), discussing hereditary and familial AD genes; the forming of neurofibrillary tangles and injury of cell caused by overphosphorylation of tau protein; and involvement of .beta.-**amyloid** proteins and **estrogens** in pathogenesis of AD.

L1 ANSWER 167 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:811096 CAPLUS
DOCUMENT NUMBER: 130:192054
TITLE: **Estrogen** protects neuronal cells from the cytotoxicity induced by acetylcholinesterase-**amyloid** complexes
AUTHOR(S): Bonnefont, Andrea B.; Munoz, Francisco J.; Inestrosa, Nibaldo C.
CORPORATE SOURCE: Facultad de Ciencias Biologicas, Departamento de Biologia Celular y Molecular, Pontificia Universidad Catolica de Chile, Santiago, Chile
SOURCE: FEBS Letters (1998), 441(2), 220-224
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The senile plaques present in Alzheimer's disease (AD) are composed of a core of **amyloid** .beta.-peptide (A.beta.) plus several proteins including acetylcholinesterase (AChE). Recently the authors found that AChE forms complexes with the A.beta. peptide in vitro and that these are more cytotoxic than A.beta. fibrils alone. Considering that **estrogen** has been reported to act as a protective agent against A.beta.-induced cytotoxicity, the effect of 17.beta.-estradiol was studied in rat pheochromocytoma (PC12) and mouse neuroblastoma (Neuro 2a) cells exposed to either A.beta. alone or AChE-A.beta. complexes. **Estrogen** showed a powerful protective effect in response to the challenge of AChE-A.beta. complexes as well as with A.beta. fibrils. This was also the case for other cytotoxic agents such as glutamate and H2O2. The authors' results suggest a common mechanism for cellular protection by **estrogen** against the toxicity of both A.beta. fibrils and AChE-A.beta. complexes, likely avoiding the free radical apoptotic pathway.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 168 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:749167 CAPLUS

DOCUMENT NUMBER: 130:151617

TITLE: Etiology and pathogenesis of Alzheimer's disease

AUTHOR(S): Farlow, Martin R.

CORPORATE SOURCE: Department of Neurology, School of Medicine, Indiana University, Indianapolis, IN, USA

SOURCE: American Journal of Health-System Pharmacy (1998), 55(Suppl. 2), S5-S10
CODEN: AHSPEK; ISSN: 1079-2082

PUBLISHER: American Society of Health-System Pharmacists

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 32 refs. The diagnosis, genetics, risk factors, neuropathol., and pathogenesis of Alzheimer's disease (AD) are discussed. AD is a degenerative brain disorder and is the leading cause of dementia. Clin. manifestations of AD are primarily the progressive loss of memory and language. Other signs and symptoms of the disease include psychiatric and behavioral disturbances and impairments in the performance of activities of daily living (ADL). To diagnose AD, other causes of dementia - some of which may be reversible - must be ruled out by lab. testing and neuroimaging. The pathogenic process that causes AD has not been fully delineated; however, it clearly leads to neuropathol. characterized by neuritic plaques, neurofibrillary tangles, and loss of cholinergic neurons in the nucleus basalis of Meynert. Genetic factors, including mutations in the **amyloid** precursor protein and the two presenilin genes, appear important in the development of early-onset familial AD, whereas the apolipoprotein E genotype influences the timing of disease onset after age 65. Genetic factors may promote or accelerate deposition of .beta.-**amyloid** protein to form plaques, as well as abnormal phosphorylation of tau protein to form neurofibrillary tangles. Several biochem. factors, such as inflammation, oxidative stress, and hormonal deficiency (**estrogen**), and other unmodifiable risk factors, notably aging, also play a role in the pathogenic process. The loss of neurons and synaptic connections is selective and causes deficiencies in cholinergic and other neurotransmitter systems, leading to cognitive dysfunction, psychiatric and behavioral disturbances, and eventual loss of ability to perform ADL. The etiol. and pathogenesis of AD are highly complex; more effective therapeutic approaches than those currently available will be needed to address these underlying factors more specifically.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 169 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:737472 CAPLUS
DOCUMENT NUMBER: 130:76348
TITLE: A novel, synergistic interaction between 17 .beta.-estradiol and glutathione in the protection of neurons against .beta.-**amyloid** 25-35-induced toxicity in vitro
AUTHOR(S): Gridley, Kelly E.; Green, Pattie S.; Simpkins, James W.
CORPORATE SOURCE: Department of Pharmacodynamics and Center for Neurobiology of Aging, College of Pharmacy, University of Florida, Gainesville, FL, 32610, USA
SOURCE: Molecular Pharmacology (1998), 54(5), 874-880
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present studies were undertaken to investigate the possibility of an interaction between 17 .beta.-estradiol (E2) and glutathione in protecting cells against the presence of .beta.-**amyloid** 25-35 (.beta.AP 25-35). The authors demonstrate that when evaluated individually, supraphysiol. concns. of either E2 (200 nM) or of reduced glutathione (GSH; 325 .mu.M) can protect SK-N-SH human neuroblastoma cells from .beta.AP 25-35 (20 .mu.M) toxicity. This dose of .beta.AP 25-35 was chosen based on the LD50 (28.9 .mu.M) obtained in the authors' earlier work. However, in the presence of 3.25 .mu.M GSH, the neuroprotective EC50 of E2 was shifted from 126 nM to 0.033 nM, approx. 4000-fold. Similarly, in primary rat cortical neurons, the addn. of GSH (3.25 .mu.M) increased the potency of E2 against .beta.AP 25-35 (10 .mu.M) toxicity, as evidenced by a shift in the EC50 values of E2 from 68 nM in the absence of GSH to 4 nM in its presence. The synergy between E2 and GSH was not antagonized by the addn. of the **estrogen** receptor antagonist, ICI 182,780. Other thiol-contg. compds. did not interact synergistically with E2, nor were any synergistic interactions obsd. between E2 and ascorbic acid or .alpha.-tocopherol. Based on these data, the authors propose an **estrogen**-receptor independent synergistic interaction between glutathione and E2 that dramatically increases the neuroprotective potency of the steroid and may provide insight for the development of new treatment strategies for neurodegenerative diseases.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 170 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:708169 CAPLUS
DOCUMENT NUMBER: 130:90634
TITLE: **Estrogen** attenuates over-expression of .beta.-**amyloid** precursor protein messenger RNA in an animal model of focal ischemia
AUTHOR(S): Shi, Jiong; Panickar, Kiran S.; Yang, Shao-Hua; Rabbani, Omid; Day, Arthur L.; Simpkins, James W.
CORPORATE SOURCE: Department of Pharmacodynamics and Center for Neurobiology of Aging, University of Florida, Gainesville, FL, 32610, USA
SOURCE: Brain Research (1998), 810(1,2), 87-92
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cerebral ischemia is a risk factor for late onset Alzheimer's disease. Since **estrogen** replacement therapy benefits the outcome of

cerebral stroke in postmenopausal women, we designed the present study to investigate the effects of **estrogen** on the expression of .beta.-**amyloid** precursor protein (APP) mRNA following focal ischemia in female rats. Female rats were ovariectomized (OVX) for two weeks. A single dose of 17.beta.-estradiol (E2) (100 .mu.g/kg) was injected s.c. two hours before a unilateral middle cerebral artery (MCA) occlusion. Brain samples were harvested from ischemic core and penumbra of cortices at one hour and twenty-four hours following MCA occlusion. The expression of APP mRNA was assessed by RT-PCR. At one hour after MCA occlusion, OVX rats had a 67.9% increase in APP mRNA in the penumbra. E2 treatment reduced this APP mRNA over-expression by 26.3% at that region. At twenty four hours following MCA occlusion, OVX rats had increases in APP mRNA of 52.9% and 57.0% in the core and penumbra, resp. E2 treatment reduced the APP mRNA over-expression by 61.0% and 48.6% in these two regions, resp. These effects appeared to reflect an interaction between hormonal environment and ischemia, since in the absence of MCA occlusion, there were no significant differences in APP mRNA expression among OVX, OVX-E2 treated and intact female rats. The present study demonstrates that **estrogen** may have an important role in reducing the over-expression of APP mRNA following focal ischemia.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 171 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:682130 CAPLUS
DOCUMENT NUMBER: 129:271503
TITLE: Regulation of **amyloid** precursor protein (APP) expression by estrogenic compounds
INVENTOR(S): Lee, Robert K. K.; Wurtman, Richard J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9843647 | A1 | 19981008 | WO 1998-US6017 | 19980326 |
| W: CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| US 6333317 | B1 | 20011225 | US 1998-49198 | 19980327 |

PRIORITY APPLN. INFO.: US 1997-42858P P 19970328

AB It has been discovered that lipophilic hormones that interact with cytosolic or nuclear receptors regulate APP expression and synthesis, through modification of APP mRNA stability and/or regulation of APP gene transcription and translation activities. These studies demonstrate that the treatment of brain cells with estrone or 17.beta.-estradiol results in a redn. in the level of APP holoprotein expression, without a concomitant change in the total level of cell protein. The redn. in the level of APP holoprotein caused by estrone or 17.beta.-estradiol is also expected to reduce the prodn. of neurotoxic APP fragments. In as much as **estrogen** deficiency in postmenopausal women is assocd. with a higher incidence of Alzheimer's disease, this discovery opens the possibility that **estrogen** therapy may prevent some of the neurodegenerative and cognitive changes assocd. with Alzheimer's disease, aging and other disease conditions assocd. with such neurodegenerative and cognitive decline.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 172 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:647127 CAPLUS
DOCUMENT NUMBER: 130:11185
TITLE: Molecular cloning of the promoter of the gene encoding the Rhesus monkey .beta.-**amyloid** precursor protein: structural characterization and a comparative study with other species
AUTHOR(S): Song, Weihong; Lahiri, Debomoy K.
CORPORATE SOURCE: Program In Medical Neurobiology, Institute of Psychiatric Research, Indianapolis, IN, 46202, USA
SOURCE: Gene (1998), 217(1-2), 151-164
CODEN: GENED6; ISSN: 0378-1119
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Abnormal regulation of transcription of the .beta.-**amyloid** precursor protein (.beta.APP) gene is implicated in the pathogenesis of Alzheimer's disease (AD). We have examd. a 17-kb genomic DNA region which contains the 5'-flanking region (promoter), first exon and intron of the .beta.APP gene of the Rhesus monkey (rh.beta.APP). A predominant transcription start site was identified 146 bp upstream of the translation initiation codon. Sequencing of 5848 bp of 5'-flanking DNA revealed the presence of multiple near consensus sequences for binding potential transcriptional regulatory factors, such as activator proteins (AP-1, AP-2), an apolipoprotein E-B1 element, **estrogen**-responsive element, heat shock element and NF-.kappa.B. The sequence of the rh.beta.APP promoter also contains several sites for the binding of proteins that serve as signal transducers and activators of transcription (STAT1) (GAS). The rh.beta.APP promoter is highly homologous to the human promoter, but less homologous to the rodents. The homol. between human and Rhesus monkey of the further upstream region gradually decreased over its length. A region of 270 bp of the human .beta.APP promoter is missing from the Rhesus monkey promoter. Structural anal. of the promoter suggests that it contains characteristics of inducible genes and sites for regulated activity by various transcription factors.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 173 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:643903 CAPLUS
DOCUMENT NUMBER: 130:33143
TITLE: **Estrogens** with an intact phenolic group prevent death of neuronal cells following glutathione depletion
AUTHOR(S): Behl, Christian; Lezoualc'h, Frank
CORPORATE SOURCE: Max-Planck-Institute of Psychiatry, Clinical Institute, Munich, 80804, Germany
SOURCE: Restorative Neurology and Neuroscience (1998), 12(2,3), 127-134
CODEN: RNNEEL; ISSN: 0922-6028
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Oxidative stress-induced neurodegeneration has been implicated in a variety of neuropsychiatric disorders including Alzheimer's disease (AD). Therefore, neuroprotection is of central interest in basic and preclin. neuroscience. Recently, we reported that the AD-assocd. **amyloid** .beta. protein can induce neuronal cell death via the generation of free radicals, oxidative stress and lipid peroxidn. The depletion of the intracellular pool of glutathione (GSH), an important intracellular antioxidant, can also induce oxidative events. Various lipophilic antioxidants, including the female sex hormone **estrogen**, can

protect neurons against oxidative cell death. Here, we report that **estrogens** prevent oxidative cell death induced by GSH depletion in murine clonal hippocampal HT22 cells and in cells of the sympathetic precursor-like cell line PC12. **Estrogens** act as free radical scavengers and inhibit the intracellular accumulation of peroxides caused by GSH depletion and, ultimately, prevent neuronal cell death. This protective activity is independent of the presence or activation of **estrogen** receptors but is dependent on the presence of an intact hydroxyl group in the steroid ring A of the **estrogen** mol. The modification or the absence of this group led to a loss of the neuroprotective activity. These data further support the important role of antioxidants in neuroprotection and may help in the design of novel antioxidant drugs.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 174 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:509114 CAPLUS
DOCUMENT NUMBER: 129:131266
TITLE: Compositions to enhance the cytoprotective effects of polycyclic phenolic compounds through the synergistic interaction with antioxidants
INVENTOR(S): Simpkins, James W.; Gridley, Kelly E.; Green, Pattie S.
PATENT ASSIGNEE(S): University of Florida Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9831381 | A1 | 19980723 | WO 1998-US963 | 19980116 |
| W: AU, CA, JP, KR | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| AU 9860306 | A1 | 19980807 | AU 1998-60306 | 19980116 |
| AU 719764 | B2 | 20000518 | | |
| US 5972923 | A | 19991026 | US 1998-7915 | 19980116 |
| EP 977578 | A1 | 20000209 | EP 1998-903560 | 19980116 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002501482 | T2 | 20020115 | JP 1998-534605 | 19980116 |

PRIORITY APPLN. INFO.:
US 1997-35537P P 19970116
US 1997-53516P P 19970723
US 1997-58104P P 19970905
WO 1998-US963 W 19980116

AB A method is provided for enhancing the cytoprotective effect of polycyclic phenolic compds. on a population of cells that involves the steps of administering a combination of polycyclic phenolic compds. and antioxidants to achieve an enhanced effect that is greater than the use of either compd. administered sep. under otherwise similar conditions. An example of an antioxidant for use in the method is glutathione (GSH) and an example of a polycyclic phenolic compd. is an **estrogen** compd. The cytoprotective effect occurs in a variety of different cell types including neuronal cells and cells of the vascular system. Effects of 17.beta.-estradiol and GSH on the toxicity induced by .beta.-**amyloid** protein on neuronal cells in culture were studied: neuroprotection provided by a 200 nM 17.beta.-estradiol was 99.9 % and 35.6 % in the presence and absence of GSH, resp.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 175 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:284766 CAPLUS
DOCUMENT NUMBER: 129:76668
TITLE: **Estrogens** influence growth, maturation, and **amyloid** .beta.-peptide production in neuroblastoma cells and in a .beta.-APP transfected kidney 293 cell line
AUTHOR(S): Chang, David; Kwan, Judy; Timiras, Paola S.
CORPORATE SOURCE: Department of Molecular and Cell Biology, University of California, Berkeley, CA, 94720-3202, USA
SOURCE: Advances in Experimental Medicine and Biology (1997), 429(Brain Plasticity: Development and Aging), 261-271
CODEN: AEMBAP; ISSN: 0065-2598
PUBLISHER: Plenum Publishing Corp.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB During development in vivo and in vitro, **estrogens**: (a) increase brain excitability, particularly in limbic structures; (b) are responsible for the maturation and cyclicity of limbic-hypothalamic interrelations; (c) enhance myelinogenesis; and (d) may act with NGF to stimulate neurite formation. In senescence, **estrogen** administration would improve memory in postmenopausal women. The absence or low levels of **estrogens** after menopause would increase prevalence of Alzheimer's dementia (AD) more in women than men, irresp. of age or ethnicity. In the present study, addn. of 17-.beta. estradiol to cultured human neuroblastoma cells affected growth slightly, but stimulated cell maturation as shown by increased tyrosine hydroxylase activity. The extracellular deposition in brain tissue and around blood vessels of the **amyloid** .beta.-peptide (A.beta.), a 4.3 kDa fragment of the larger integral membrane protein, .beta.-**amyloid** precursor protein (.beta.-APP), is considered an important characteristic of AD. We investigated whether 17-.beta. estradiol may influence the formation of the A.beta. (thus the abnormal accumulation of **amyloid** proteins) in neuroblastoma cells and in a .beta.-APP transfected human kidney 293 cell line. Two doses of 17 .beta.-estradiol were added to the cultures of both cell lines. Cells were grown until confluence, metabolically labeled with 35S-methionine, immunopptd. with the rabbit antiserum R1282, gel electrophoresed and autoradiographed in order to compare levels of A.beta. under the different estradiol concns. While in neuroblastoma cells, levels of A.beta. were only slightly reduced after estradiol and a dose-effect relationship with the hormone could not be demonstrated, in the 293 cells, A.beta. band intensity decreased as concn. of estradiol increased. These data support the role of **estrogen** in normal and abnormal brain metab. and suggest potential hormonal interventions which may reduce or prevent the formation of **amyloid** deposits that occur in AD.
REFERENCE COUNT: 67 THERE ARE 67 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 176 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:243667 CAPLUS
DOCUMENT NUMBER: 129:730
TITLE: **Estrogen** reduces neuronal generation of Alzheimer .beta.-**amyloid** peptides
AUTHOR(S): Xu, Huaxi; Gouras, Gunnar K.; Greenfield, Jeffrey P.; Vincent, Bruno; Naslund, Jan; Mazzarelli, Louis; Fried, Gabriel; Jovanovic, Jasmina N.; Seeger, Mary; Relkin, Norman R.; Liao, Fang; Checler, Frederic; Buxbaum, Joseph D.; Chait, Brian T.; Thinakaran, Gopal.; Sisodia, Sangram S.; Wang, Rong; Greengard,

Paul; Gandy, Sam
CORPORATE SOURCE: Fisher Cent. Res. Alzheimer Dis., Rockefeller Univ., New York, NY, 10021, USA
SOURCE: Nature Medicine (New York) (1998), 4(4), 447-451
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease (AD) is characterized by the accumulation of cerebral plaques composed of 40- and 42-amino acid .beta.-**amyloid** (A.beta.) peptides, and autosomal dominant forms of AD appear to cause disease by promoting brain A.beta. accumulation. Recent studies indicate that postmenopausal **estrogen** replacement therapy may prevent or delay the onset of AD. Here we present evidence that physiol. levels of 17.beta.-estradiol reduce the generation of A.beta. by neuroblastoma cells and by primary cultures of rat, mouse and human embryonic cerebrocortical neurons. These results suggest a mechanism by which **estrogen** replacement therapy can delay or prevent AD.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 177 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:176098 CAPLUS
DOCUMENT NUMBER: 128:213735
TITLE: Method of screening for side effects of anticonceptives or **estrogen** and/or progesterone replacements or supplements
INVENTOR(S): Kluft, Cornelis; Emeis, Josephus Jan
PATENT ASSIGNEE(S): Nederlandse Organisatie Voor Toegepast-Natuurwetenschappelijk Onderzoek TNO, Neth.; Kluft, Cornelis; Emeis, Josephus Jan
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9810293 | A1 | 19980312 | WO 1996-NL350 | 19960906 |
| W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9669475 | A1 | 19980326 | AU 1996-69475 | 19960906 |
| AU 733553 | B2 | 20010517 | | |
| EP 931263 | A1 | 19990728 | EP 1996-930447 | 19960906 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002505736 | T2 | 20020219 | JP 1998-512508 | 19960906 |
| NO 9901034 | A | 19990430 | NO 1999-1034 | 19990303 |
| US 2002110523 | A1 | 20020815 | US 2001-985561 | 20011105 |

PRIORITY APPLN. INFO.: WO 1996-NL350 W 19960906
US 1999-254348 A3 19990323

AB A method for screening for neg. side effects of a sex steroid compd. or compn. in a subject, by carrying out an assay on the subject or on a sample derived from the subject detg. whether an increase on the level of

an acute phase reactant (i.e., blood proteins which can increase in concn. by 25% or more in the first 7 days following tissue damage) or a metabolic deriv. thereof has occurred since applying the compd. or compn. to the subject. These acute phase reactants are selected from the group consisting of pos. Acute Phase Reactants (APRs) with the exclusion of ceruloplasmin and coagulation/thrombosis assocd. factors, whereby an increase in the level of the acute phase reactant is indicative of neg. side effects. A sex steroid compd. or compn. is claimed characterized by a lower increase in APR level as detd. in a manner according to the invention than a third generation oral contraceptive, said compd. or compn. not being a second generation oral contraceptive.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 178 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:169417 CAPLUS
DOCUMENT NUMBER: 128:226257
TITLE: Compositions and methods modulating **amyloid** precursor protein for treatment of neurological disorders and neurodegenerative diseases, including Alzheimer's disease
INVENTOR(S): Lee, Robert K. K.; Wurtman, Richard J.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9809523 | A1 | 19980312 | WO 1997-US15321 | 19970905 |
| W: CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 1006798 | A1 | 20000614 | EP 1997-941386 | 19970905 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.:
US 1996-25507P P 19960905
US 1997-33765P P 19970115
WO 1997-US15321 W 19970905

AB It has been discovered that the stimulation of .beta.-adrenergic receptors, which activate cAMP formation, give rise to increased APP and GFAP synthesis in astrocytes. Hence, the in vitro or in vivo exposure of neuronal cells to certain compns. comprising .beta.-adrenergic receptor ligands or agonists, including, e.g., norepinephrine, isoproterenol and the like, increases APP mRNA transcription and consequent APP overprodn. These increases are blocked by .beta.-adrenergic receptor antagonists, such as propranolol. The in vitro or in vivo treatment of these cells with 8Br-cAMP, prostaglandin E2 (PG E2), forskolin, and nicotine ditartrate also increased APP synthesis, including an increase in mRNA and holoprotein levels, as well as an increase in the expression of glial fibrillary acidic protein (GFAP). Compns. and methods are disclosed of regulating APP overexpression and mediating reactive astrogliosis through cAMP signaling or the activation of .beta.-adrenergic receptors. It has further been found that the increase in APP synthesis caused by 8Br-cAMP, PG E2, forskolin, or nicotine ditartrate is inhibited by immunosuppressants or anti-inflammatory agents, such as cyclosporin A, and FK-506 (tacrolimus), as well as ion-channel modulators, including ion chelating agents such as EGTA, or calcium/calmodulin kinase inhibitors, such as KN93. The present invention has broad implications in the alleviation, treatment, or prevention of neurol. disorders and

neurodegenerative diseases, including Alzheimer's disease.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 179 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:168130 CAPLUS
DOCUMENT NUMBER: 128:279070
TITLE: Nuclear **estrogen** receptor-independent neuroprotection by estratrienes: a novel interaction with glutathione
AUTHOR(S): Green, P. S.; Gridley, K. E.; Simpkins, J. W.
CORPORATE SOURCE: Center for the Neurobiology of Aging and the Department of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, FL, 32610, USA
SOURCE: Neuroscience (Oxford) (1998), 84(1), 7-10
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Post-menopausal **estrogen** replacement therapy is assocd. with a redn. in the risk of Alzheimer's disease and has been reported to improve cognitive functioning in several small clin. trials. The present study evaluates the dependence of estrogenic neuroprotection on the presence of **estrogen** receptors using the murine neuronal cell line, HT-22, exposed to the neurotoxic .beta.-**amyloid** peptide. These cells lack functional **estrogen** receptors. The **amyloid** peptide killed 50-60% of these cells and concurrent treatment with either of three estratrienes, .beta.-estradiol, .alpha.-estradiol, or estratrien-3-ol, resulted in a dose-dependent protection. The potency of this **estrogen** neuroprotection was dependent on the presence of glutathione in the culture media. The presence of reduced glutathione in the media increases the neuroprotective potency of **estrogens** by an av. of 400-fold. These results demonstrate that a nuclear **estrogen** receptor is not necessary for the neuroprotective actions of **estrogens**; however, the presence of an appropriate antioxidant in the extracellular milieu is needed for estratriene neuroprotection at physiol. and pharmacol. relevant doses. These data suggest the possibility of combined **estrogen**-antioxidant therapy for neurodegenerative diseases such as Alzheimer's disease.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 180 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:25162 CAPLUS
DOCUMENT NUMBER: 128:97725
TITLE: Therapeutic methods and compositions using R-ibuprofen
INVENTOR(S): Xiaotao, Qian; Hall, Stephen D.
PATENT ASSIGNEE(S): Advanced Research and Technology Institute, USA; Xiaotao, Qian; Hall, Stephen D.
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9748391 | A2 | 19971224 | WO 1997-US10762 | 19970620 |
| WO 9748391 | A3 | 19980129 | | |

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,

LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

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| AU 9736415 | A1 | 19980107 | AU 1997-36415 | 19970620 |
| US 6255347 | B1 | 20010703 | US 1997-879870 | 19970620 |

PRIORITY APPLN. INFO.: US 1996-20248P P 19960621
WO 1997-US10762 W 19970620

AB The invention concerns the use of ibuprofen, a non-steroid anti-inflammatory drug, in the treatment of disease. More particularly, it has been discovered that the R-enantiomer of ibuprofen, previously thought to be inactive, may be used as an antineoplastic agent by inhibiting protein kinase C (PKC .alpha.) translocation from cytosol to nuclear and microsomal membranes and also in the prophylactic and therapeutic treatment of Alzheimer's and Alzheimer's related diseases by forming R-Ibuprofen-DAG (diacylglycerols) which activate PKC and thereby promote secretion of APP (**amyloid** precursor protein).

L1 ANSWER 181 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:24021 CAPLUS
DOCUMENT NUMBER: 128:135969
TITLE: Recent developments in the pathophysiology and pharmacotherapy of Alzheimer's disease: part II
AUTHOR(S): Felician, Olivier J.; Sandson, Thomas A.
CORPORATE SOURCE: Behavioral Neurology Unit, Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, 02215, USA
SOURCE: Drugs of Today (1997), 33(9), 665-671
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: J. R. Prous, S.A.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 50 refs. Alzheimer's disease (AD) has become a major public health concern as the population ages. Improved understanding of the pathogenesis of AD has provided the rational basis for numerous pharmacol. interventions. Treatment with second generation acetylcholinesterase inhibitors has been shown to result in mild symptomatic benefit. Exptl. and epidemiol. data suggest that **estrogen** replacement therapy might provide addnl. symptomatic benefit and possibly decrease the rate of disease progression. Inflammatory mechanisms and oxidative stress appear to be directly involved in the pathogenesis of AD, and antiinflammatory and antioxidant compds. are being tested. Medications directly targeting abnormalities of **amyloid** metab. in AD are also under development. This article reviews these and other recent advances in the pharmacotherapy of AD.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 182 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:804642 CAPLUS
DOCUMENT NUMBER: 128:70935
TITLE: **Estrogens** stabilize mitochondrial function and protect neural cells against the pro-apoptotic action of mutant presenilin-1
AUTHOR(S): Mattson, Mark P.; Robinson, Nic; Guo, Qing
CORPORATE SOURCE: Sanders-Brown Res. Center Aging, Dep. Anatomy and Neurobiology, Univ. Kentucky, Lexington, KY, 40536, USA
SOURCE: NeuroReport (1997), 8(17), 3817-3821
CODEN: NERPEZ; ISSN: 0959-4965

PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mutations in presenilin-1 (PS-1) account for approx. half the cases of autosomal dominant early-onset Alzheimer's disease (AD). Recent data indicate that PS-1 mutations may render neurons vulnerable to apoptosis induced by various insults. We now report that 17.beta.-estradiol, which appears to reduce the risk of sporadic AD, protects cultured PC12 cells expressing mutant PS-1 against apoptosis induced by trophic factor withdrawal (TFW) and exposure to **amyloid** .beta.-peptide 25-35 (A.beta.). Estriol also provided significant protection against apoptosis induced by TFW and A.beta., whereas corticosterone was ineffective. 17.beta.-Estradiol prevented decreases in mitochondrial transmembrane potential and energy charge/redox state following exposure of cells to TFW and A.beta. in control cell lines and lines expressing mutant PS-1, suggesting an action in the apoptotic pathway upstream of mitochondrial alterations. A.beta. caused an increase in mitochondrial reactive oxygen species which was enhanced by mutant PS-1, and suppressed by 17.beta.-estradiol. The ability of 17.beta.-estradiol to preserve mitochondrial function, suppress oxidative stress, and counteract the pro-apoptotic actions of mutant PS-1 suggests a generalized neuroprotective action of **estrogens** in both sporadic and inherited forms of AD.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 183 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:795596 CAPLUS
DOCUMENT NUMBER: 128:97835
TITLE: Low concentrations of estradiol reduce .beta.-**amyloid** (25-35)-induced toxicity, lipid peroxidation and glucose utilization in human SK-N-SH neuroblastoma cells
AUTHOR(S): Gridley, Kelly E.; Green, Pattie S.; Simpkins, James W.
CORPORATE SOURCE: College of Pharmacy, Box, Department of Pharmacodynamics and Center for Neurobiology of Aging, University of Florida, Gainesville, FL 32610, 100487, USA
SOURCE: Brain Research (1997), 778(1), 158-165
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present studies were undertaken to det. the role of physiol. relevant concns. of **estrogens** on **amyloid**-induced changes in cell viability, metabolic demands, and lipid peroxidn. in response to the toxic fragment of .beta.-**amyloid** (.beta.AP 25-35). To this end, SK-N-SH human neuroblastoma cells were exposed to .beta.AP 25-35 or .beta.AP 25-35 plus 17.beta.-estradiol, and cell viability, media glucose use and lactate prodn. were measured at time points ranging from 3 to 15 h for examn. of acute effects, or at 48 and 72 h time points for chronic effects. Addn. of .beta.AP 25-35 to SK-N-SH cells decreased the no. of viable cells from 5 at 3 h to 35 at 15 h when compared to vehicle controls. Chronic treatment for 48 and 72 h caused decreases in viable cell no. of 70 and 65, resp. Paradoxically, both glucose utilization and lactate prodn. were found to be increased for the .beta.AP-treated cells. Concomitant **estrogen** treatment was found to be neuroprotective, as the severity of the insult on cell viability was decreased by 40 at 15 h and up to 71 at 72 h. Likewise, the addn. of 17.beta.-estradiol decreased both the glucose use and lactate prodn. of the cells. Chronic treatment with .beta.AP caused increases in lipid peroxidn. over vehicle

treated controls of 82 and 78 at 48 and 72 h, resp., while decreases in peroxidn. of 48 were seen with simultaneous **estrogen** treatment. These results indicate that the neuroprotective effects of **estrogens** against .beta.AP-induced toxicity are due in part to their capability to decrease lipid peroxidn. and may addnl. be attributable to decreasing the metabolic load of the cell.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 184 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:774254 CAPLUS
DOCUMENT NUMBER: 128:71065
TITLE: 17.beta.-Estradiol attenuates oxidative impairment of synaptic Na+/K+-ATPase activity, glucose transport, and glutamate transport induced by **amyloid** .beta.-peptide and iron
AUTHOR(S): Keller, Jeffrey N.; Germeyer, Ariane; Begley, James G.; Mattson, Mark P.
CORPORATE SOURCE: Sanders-Brown Research Center on Aging, University of Kentucky, Lexington, KY, USA
SOURCE: Journal of Neuroscience Research (1997), 50(4), 522-530
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Synapse loss, deposits of **amyloid** .beta.-peptide (AD), impaired energy metab., and cognitive deficits are defining features of Alzheimer's disease (AD). **Estrogen** replacement therapy reduces the risk of developing AD in postmenopausal women. Because synapses are likely sites for initiation of neurodegenerative cascades in AD, we tested the hypothesis that **estrogens** act directly on synapses to suppress oxidative impairment of membrane transport systems. Exposure of rat cortical synaptosomes to A.beta.25-35 (AP) and FeSO4 induced membrane lipid peroxidn. and impaired the function of the plasma membrane Na+/K+-ATPase, glutamate transporter, and glucose transporter. Pretreatment of synaptosomes with 17.beta.-estradiol or estriol largely prevented impairment of Na+/K+-ATPase activity, glutamate transport, and glucose transport; other steroids were relatively ineffective. 17.beta.-Estradiol suppressed membrane lipid peroxidn. induced by AP and FeSO4, but did not prevent impairment of membrane transport systems by 4-hydroxynonenal (a toxic lipid peroxidn. product), suggesting that an antioxidant property of 17.beta.-estradiol was responsible for its protective effects. By suppressing membrane lipid peroxidn. in synaptic membranes, **estrogens** may prevent impairment of transport systems that maintain ion homeostasis and energy metab., and thereby forestall excitotoxic synaptic degeneration and neuronal loss in disorders such as AD and ischemic stroke.

REFERENCE COUNT: 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 185 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:767218 CAPLUS
DOCUMENT NUMBER: 128:84428
TITLE: **Estrogen** replacement therapy for the prevention and treatment of Alzheimer's disease
AUTHOR(S): Henderson, Victor W.
CORPORATE SOURCE: Departments of Neurology and Psychology, the School of Gerontology, University of Southern California, Los Angeles, CA, USA
SOURCE: CNS Drugs (1997), 8(5), 343-351
CODEN: CNDREF; ISSN: 1172-7047

PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 89 refs. Alzheimer's disease is characterized by the gradual but progressive loss of memory and other cognitive abilities. Pathol. features include the accumulation of neurofibrillary tangles, neuritic plaques and .beta.-**amyloid** protein within vulnerable regions of the brain. A no. of actions of **estrogen** have the potential to affect brain function and influence the pathol. of Alzheimer's disease. Early-onset Alzheimer's disease is a relatively infrequent disorder which is usually inherited in an autosomal dominant manner. However, for late-onset illness, it is likely that several genetic and environmental factors are pathogenetically important. A no. of epidemiol. studies link postmenopausal hormonal replacement therapy to a reduced risk of developing Alzheimer's disease. **Estrogen** can affect cognition and mood, and a no. of generally small intervention trials suggest that **estrogen** improves cognitive skills among women with Alzheimer's disease. However, most treatment studies have not been conducted in a methodol. rigorous fashion. There are no firm data on different **estrogen** prepns. and dosages or on the role of progestins in the prevention and treatment of Alzheimer's disease in women, and no data support the use of **estrogen** for this disorder in men.
REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 186 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:723830 CAPLUS
DOCUMENT NUMBER: 128:30497
TITLE: **Estrogen** blocks neurotoxic effects of .beta.-**amyloid** (1-42) and induces neurite extension on B103 cells
AUTHOR(S): Mook-Jung, Inhee; Joo, Insoo; Sohn, Seonghyang; Jae Kwon, Hyuk; Huh, Kyoon; Whan Jung, Min
CORPORATE SOURCE: School of Medicine, Department of Neurology, Ajou University, Suwon, 442-749, S. Korea
SOURCE: Neuroscience Letters (1997), 235(3), 101-104
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Clin. studies have shown that **estrogen** replacement therapy is assocd. with reduced risk of Alzheimer's disease (AD). The authors tested whether or not **estrogen** blocks neurotoxic effects of .beta.-**amyloid** (1-42) (A.beta.1-42) on cultured B103 cells. A.beta.1-42 (1 .mu.M) induced typical necrotic cell death, as revealed by light and electron microscopic examns. Co-administration of **estrogen** not only blocked A.beta.1-42 toxicity to a large degree, but also enhanced neurite extension. Pretreatment with **estrogen** was even more effective in blocking A.beta.1-42 toxicity. When added 18 h after the beginning of A.beta.1-42 treatment, **estrogen** was still effective in halting the progress of cell death and enhancing neurite extension. The protection against A.beta.1-42-induced neuronal death by **estrogen** was unlikely due to a blockade of lipid peroxidn. injury, since **estrogen** completely failed to attenuate ferrous chloride-induced cell death. These results demonstrate that **estrogen** blocks A.beta.1-42-induced neurotoxicity and enhances neurite extension on B103 cells, both of which may well be underlying mechanisms of beneficial effects of **estrogen** in AD.
REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 187 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:710055 CAPLUS
DOCUMENT NUMBER: 127:357428
TITLE: Current concepts in the pathogenesis of Alzheimer's disease
AUTHOR(S): Carr, D. B.; Goate, A.; Morris, J. C.
CORPORATE SOURCE: Division of Geriatrics and Gerontology, Washington University, St. Louis, MO, 63108, USA
SOURCE: American Journal of Medicine (1997), 103(3(A)), 3S-10S
CODEN: AJMEAZ; ISSN: 0002-9343
PUBLISHER: Excerpta Medica
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 89 refs. Alzheimer's disease (AD) affects a large proportion of the increasingly aging population of this country, with prevalence rates as high as 47% for those >85 yr old and a total annual cost approaching $70 billion. There is no currently validated test for detection of dementia of the Alzheimer type (DAT). Because of this and the insidious onset of the disease, the diagnosis may be missed by primary care physicians. Cerebral extracellular .beta.-**amyloid** deposition as senile plaques and intraneuronal neurofibrillary tangles appear to represent crit. processes in the development of AD; however, whether and the extent to which these may also occur in nondemented aging is uncertain. Tangles occur primarily in medial temporal lobe structures (hippocampus, entorhinal cortex, and amygdala), and tangle d. correlates with dementia severity. Plaques are diffusely distributed throughout the cerebral cortex, and are the neuropathol. hallmark of the disease. Aging is the primary risk factor for AD. After controlling for differential life expectancy, female sex still appears to be an addnl. risk factor. There may be a genetic component, in some cases based on family and twin studies. Allelic variation in the apolipoprotein E (Apo E) gene located on chromosome 19 represents another important risk factor. However, the diversity of gene mutations apparently responsible for the various forms of AD suggest that the disease is genetically heterogeneous. AD may be conceptualized as an imbalance between neuronal injury and repair. Oxygen free radicals may be involved in the crosslinking process of .beta.-**amyloid** aggregation, and antioxidants may represent a potential intervention. There may be a role for heavy metals in the pathogenesis of AD, but this remains controversial. Work continues toward possibly a cure or prevention, but palliation is more likely; the results of trials of anti-inflammatory agents, **estrogen**, and antioxidant therapy are anticipated in the near future.
REFERENCE COUNT: 89 THERE ARE 89 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 188 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:633928 CAPLUS
DOCUMENT NUMBER: 127:317682
TITLE: Female protein, amyloidosis, and hormonal carcinogenesis in Turkish hamster: differences from Syrian hamster
AUTHOR(S): Coe, John E.; Cieplak, W.; Hadlow, W. J.; Ross, M. J.
CORPORATE SOURCE: Lab. Persistent Viral Diseases, Rock Mountain Laboratories, National Inst. Allergy and Infectious Diseases, Hamilton, MT, 59840, USA
SOURCE: American Journal of Physiology (1997), 273(3, Pt. 2), R934-R941
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Syrian hamster (Mesocricetus auratus) has been widely used as an

exptl. animal and is a unique model for three sex hormone-regulated events: (1) **estrogen**-initiated renal carcinogenesis, (2) sex-limited expression of amyloidosis, a ubiquitous disease, and (3) sex hormone control of a serum **amyloid** P component (SAP) called female protein (FP). In this study, the authors evaluated the closely related Turkish hamster (Mesocricetus brandti) for these three events and found some very different responses: (1) **estrogen**-initiated renal carcinogenesis was not found in Turkish hamster, (2) amyloidosis was not sex limited and actually was a rare disease in the Turkish hamster, and (3) Turkish hamsters did express a sex-limited-SAP-FP in serum that was antigenically identical and structurally very similar (97.5%) to Syrian hamster SAP-FP. However, acute phase regulation of SAP-FP synthesis was different, and serum levels of this pentraxin were much lower than those found in the Syrian hamster. In contrast to findings in the Syrian hamster, hepatic tumors were relatively common in normal and esp. in **estrogen**-treated Turkish hamsters. Therefore, although they are closely related, these two Mesocricetus hamster species have markedly dissimilar responses to sex hormones.

L1 ANSWER 189 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:629099 CAPLUS
DOCUMENT NUMBER: 127:229742
TITLE: **Estrogens** and brain function
AUTHOR(S): Honjo, Hideo; Iwasa, Koichi; Urabe, Mamoru
CORPORATE SOURCE: Sanfujinkagaku, Kyoto-furitsu Ika Daigaku, Kyoto, 602, Japan
SOURCE: Hormone Frontier in Gynecology (1997), 4(3), 235-247
CODEN: HFGYFH; ISSN: 1340-220X
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 34 refs., on **estrogen** actions on brain, discussing anti-depressive effect, improvement of memory function, increase of blood flow, activation of neurons and neuroglia, and inhibition of **amyloid** accumulation. **Estrogen** replacement therapy for Alzheimer's disease is also discussed.

L1 ANSWER 190 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:567332 CAPLUS
DOCUMENT NUMBER: 127:215266
TITLE: Fundamental role for **estrogens** in cognition and neuroprotection
AUTHOR(S): Simpkins, James W.; Green, Pattie S.; Gridley, Kelly E.
CORPORATE SOURCE: Department of Pharmacodynamics and the Center for the Neurobiology of Aging, University of Florida, Gainesville, FL, 32610, USA
SOURCE: Pharmacological Treatment of Alzheimer's Disease (1997), 503-523. Editor(s): Brioni, Jorge D.; Decker, Michael W. Wiley: New York, N. Y.
CODEN: 64YGA4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with 90 refs. The topics discussed include: the role of **estrogens** in cognition, memory, and neurodegeneration; **estrogen** and the cholinergic system; neurotrophins as mediators of the neuroprotective effects of **estrogens**; neuroprotective effects of **estrogens** in vitro; and **estrogens** and .beta.-**amyloid** peptide.

L1 ANSWER 191 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:471916 CAPLUS

DOCUMENT NUMBER: 127:185100
TITLE: From molecular structure to Alzheimer therapy
AUTHOR(S): Giacobini, Ezio
CORPORATE SOURCE: Department of Geriatrics, University Hospitals of Geneva, Medical School, University of Geneva, Geneva, CH-1226, Switz.
SOURCE: Japanese Journal of Pharmacology (1997), 74(3), 225-241
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 87 refs. Clin. trials in the USA, Japan and Europe have confirmed the hypothesis that a steady state increase of acetylcholine resulting from cholinesterase inhibition in the brain results in an improvement of cognitive function in mild to moderate Alzheimer disease (AD) patients. During the last decade, a systematic effort to develop a pharmacol. treatment for AD has resulted in two drugs being registered for the first time in the USA and Europe for this specific indication. Both are cholinesterase inhibitors (ChEI). Based on these first pos. results, several second generation ChEI are being developed. An addnl. effect of certain ChEI is to maintain cognitive function at a const. level during a 6 mo to one year period of treatment as compared to placebo. It is possible that the drug effect is one of slowing down cognitive deterioration. Comparison of clin. effects of 5 ChEI demonstrates a rather similar magnitude of improvement. For some drugs, this may represent a limit, while for others it may be possible to increase the benefit further. To maximize and prolong pos. drug effects, it is important to start early and adjust the dosage during the treatment. Other strategies may involve combinations with other cholinergic drugs such as muscarinic or nicotinic agonists. A second important class of drugs which is being developed is that of muscarinic m1 agonists. However, their clin. use is still limited by side effects. The increased knowledge and recognition of the beta-**amyloid** mol. as a central focus of AD pathol. has strongly stimulated research with the hope of finding ways of influencing its processing and deposition. At this point, no product in this line of development has reached clin. trial level. Other pharmacol. approaches are related to preventive and neuroprotective interventions (**estrogens**, anti-oxidants and anti-inflammatories). In conclusion, given the relatively short time of research in this field, results are encouraging.

L1 ANSWER 192 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:364411 CAPLUS
DOCUMENT NUMBER: 127:45028
TITLE: The epidemiology of **estrogen** replacement therapy and Alzheimer's disease
AUTHOR(S): Henderson, Victor W.
CORPORATE SOURCE: Departments of Neurology (Division of Cognitive Neuroscience and Neurogerontology) and Psychology, School of Gerontology, University of Southern California, Los Angeles, CA, USA
SOURCE: Neurology (1997), 48(5, Suppl. 7), S27-S35
CODEN: NEURAI; ISSN: 0028-3878
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 142 refs. The burden of Alzheimer's disease (AD) falls more heavily on women than men. It is hypothesized that plummeting levels of circulating **estrogens** after the menopause increase a woman's risk for this disorder and, conversely, that **estrogen** replacement therapy may lower the risk for dementia due to AD. A no. of

estrogenic properties support the biol. credibility of this hypothesis. **Estrogen** interacts with neurotrophins and neurotransmitter systems relevant to AD and in some model systems **estrogen** modulates synaptic plasticity. Effects on .beta.-**amyloid** and apolipoprotein E may be esp. germane to putative protective effects. **Estrogen** also may blunt neurotoxic consequences of the stress response mediated by the hypothalamic-pituitary-adrenal axis, augment cerebral glucose utilization, and enhance cerebral blood flow. Clin. studies of postmenopausal women suggest beneficial **estrogen** effects on specific cognitive skills, and small preliminary trials of **estrogen** replacement in women with AD support claims of clin. meaningful efficacy. Consistent with the **estrogen** hypothesis, cross-sectional studies imply that postmenopausal **estrogen** use could be assocd. with a lower risk for AD. Several recent epidemiol. studies in which information on **estrogen** replacement therapy was collected prospectively further support this contention, with a dose-response relation evident in some reports. Because **estrogen** users tend to differ from nonusers in a no. of lifestyle characteristics, convincing demonstration of putative protective effects could best come from randomized, placebo-controlled, primary intervention trials. For the present, however, the issue of **estrogen** efficacy in lowering a woman's risk for AD remains unsettled.

REFERENCE COUNT: 142 THERE ARE 142 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 193 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:272938 CAPLUS
DOCUMENT NUMBER: 126:338954
TITLE: Neuroprotection against oxidative stress by **estrogens**: structure-activity relationship
AUTHOR(S): Behl, Christian; Skutella, Thomas; Lezoualc'h, Frank; Post, Anke; Widmann, Martina; Newton, Christopher J.; Holsboer, Florian
CORPORATE SOURCE: Max Planck Institute of Psychiatry, Clinical Institute, Munich, 80804, Germany
SOURCE: Molecular Pharmacology (1997), 51(4), 535-541
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Oxidative stress-induced neuronal cell death has been implicated in different neurol. disorders and neurodegenerative diseases; one such ailment is Alzheimer's disease. Using the Alzheimer's disease-assocd. **amyloid** .beta. protein, glutamate, hydrogen peroxide, and buthionine sulfoximine, the authors investigated the neuroprotective potential of **estrogen** against oxidative stress-induced cell death. The authors show that 17.beta.-estradiol, its nonestrogenic stereoisomer, 17.alpha.-estradiol, and some estradiol derivs. can prevent intracellular peroxide accumulation and, ultimately, the degeneration of primary neurons, clonal hippocampal cells, and cells in organotypic hippocampal slices. The neuroprotective antioxidant activity of **estrogens** is dependent on the presence of the hydroxyl group in the C3 position on the A ring of the steroid mol. but is independent of an activation of **estrogen** receptors.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 194 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:243048 CAPLUS
DOCUMENT NUMBER: 126:272517
TITLE: Effects of hormone replacement therapy on serum

**amyloid** P component in postmenopausal women

AUTHOR(S): Hashimoto, Shigeru; Katou, Mitsunori; Dong, Yuzhen; Murakami, Kouichi; Terada, Susumu; Inoue, Masaki

CORPORATE SOURCE: Department of Obstetrics and Gynecology, School of Medicine, Kanazawa University, Kanazawa, 920, Japan

SOURCE: Maturitas (1997), 26(2), 113-119
CODEN: MATUDK; ISSN: 0378-5122

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pentraxin serum **amyloid** P component (SAP) is a 9.5S.alpha. 1-glycoprotein and it has recently been found to be deposited in atherosclerotic lesions or neurofibrillary tangles, which are related to the aging process and Alzheimer's disease. The level of SAP was measured by micro single radial-immunodiffusion. Sample sera were obtained from 420 healthy humans, from newborn to 86 yr old. The changes in SAP during the menstrual cycle were investigated in 6 women that were 20-21 yr. Fifty of the postmenopausal women, suffering from climacteric symptoms, were administered either conjugated **estrogen** (E), or dehydroepiandrosterone (DHEA). The SAP levels increased with age, being 1.12 mg/dL in neonates, and 6.15 mg/dL in persons over 80 yr. The SAP level in the females between 15 and 49 yr (3.32 mg/dL) was significantly lower than that in the males in the same age group (5.19 mg/dL). The SAP level in the follicular phase was significantly lower than that in menstrual phase (menstrual: 4.36 mg/dL vs. follicular: 2.61 mg/dL). In the postmenopausal women that were administered E (1.25 mg/day), the SAP decreased significantly from the prelevel of 5.64 mg/dL to 4.26 mg/dL on the 14th day. In the postmenopausal women that were administered DHEA (60 mg/day), the SAP increased rapidly from the prelevel of 4.97 mg/dL to 6.17 mg/dL on the 21st day. SAP seems to be a marker that can monitor the effect of hormone replacement therapy.

L1 ANSWER 195 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1997:204238 CAPLUS

DOCUMENT NUMBER: 126:195255

TITLE: Use of non-**estrogen** polycyclic phenol compounds for the manufacture of a medicament for conferring neuroprotection to cells

INVENTOR(S): Simpkins, James W.; Green, Patti S.; Gordon, Katherine

PATENT ASSIGNEE(S): University of Florida Research Foundation, Incorporated, USA

SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 9

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| RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2227634 | AA | 19970206 | CA 1996-2227634 | 19960724 |
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PRIORITY APPLN. INFO.: US 1995-1394P P 19950724
US 1996-685574 A3 19960724

WO 1996-US12146 W 19960724

AB Non-**estrogen** compds. having a terminal phenol group in a structure contg. at least a second ring and having a mol. wt. of less than 1000 Daltons (e.g. naphthols, phenanthrenes or steroids) are used for the manuf. of a medicament for conferring neuroprotection to cells in a subject.

L1 ANSWER 196 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:727202 CAPLUS
DOCUMENT NUMBER: 126:70328
TITLE: Estradiol protects against .beta.-**amyloid** (25-35)-induced toxicity in SK-N-SH human neuroblastoma cells
AUTHOR(S): Green, Pattie S.; Gridley, Kelly E.; Simpkins, James W.
CORPORATE SOURCE: Department of Pharmacodynamics and the Center for Neurobiology of Aging, University of Florida, Gainesville, FL, 32610, USA
SOURCE: Neuroscience Letters (1996), 218(3), 165-168
CODEN: NELED5; ISSN: 0304-3940
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Estrogen**-replacement therapy has been assocd. with a reduced incidence of Alzheimer's disease (AD) and improved cognition in several small open clin. trials. We assessed the possibility that **estrogens** may reduce toxicity of .beta.-**amyloid** (A.beta.) by testing the effects of .beta.-estradiol on the toxicity of the neurotoxic fragment of .beta.-**amyloid** (A.beta. 25-35) in SK-N-SH neuroblastoma cells. A.beta. 25-35 caused a dose-dependent death in SK-N-SH cells with a LD50 of 28.9 .mu.M. In cultures simultaneously exposed to 20 .mu.M A.beta. and 17 .beta.-estradiol (2 nM), A.beta.-induced toxicity was reduced by 83 and 51% in two sep. studies. Further studies show that 0.2 nM 17.beta.-estradiol was as effective as the 2 nM concn. 17.alpha.-Estradiol (2 nM) conferred neuroprotection equiv. to that of 17.beta.-estradiol. These data support the hypothesis that **estrogens** reduce .beta.-**amyloid** toxicity and this may help explain the beneficial effects of **estrogens** in AD.

L1 ANSWER 197 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:542649 CAPLUS
DOCUMENT NUMBER: 125:186177
TITLE: Effect of **estrogen** during menopause on risk and age at onset of Alzheimer's disease
AUTHOR(S): Tang, Ming-Xin; Jacobs, Diane; Stern, Yaakov; Marder, Karen; Schofield, Peter; Gurland, Barry; Andrews, Howard; Mayeux, Richard
CORPORATE SOURCE: Columbia Univ., Gertrude H Sergievsky Cent., New York, NY, 10032, USA
SOURCE: Lancet (1996), 348(9025), 429-432
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Lancet
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Estrogen** use by postmenopausal women has many health benefits, but findings on the effect of **estrogen** in Alzheimer's disease are conflicting. **Estrogen** promotes the growth and survival of cholinergic neurons and could decrease cerebral **amyloid** deposition, both of which may delay the onset or prevent Alzheimer's disease. To investigate whether use of **estrogen** during the postmenopausal period affects the risk of Alzheimer's disease, the authors studied 1124 elderly women who were initially free of Alzheimer's disease,

Parkinson's disease, and stroke, and who were taking part in a longitudinal study of aging and health in a New York City community. Relative risks and age-at-onset distributions were calcd. from simple and adjusted Cox proportional hazards models. Std. annual clin. assessments and criterion-based diagnoses were used in follow-up (range 1-5 yr). Overall, 156 (12.5%) women reported taking **estrogen** after onset of menopause. The age at onset of Alzheimer's disease was significantly later in women who had taken **estrogen** than in those who did not and the relative risk of the disease was significantly reduced (9.156 [5.8%] **estrogen** users vs. 158/968 [16.3%] nonusers; 0.40 [95% CI 0.22-0.85]), even after adjustment for differences in education, ethnic origin, and apolipoprotein-E genotype. Women who had used **estrogen** for longer than 1 yr had a greater redn. in risk; none of 23 women who were taking **estrogen** at study enrollment has developed Alzheimer's disease. **Estrogen** use in postmenopausal women may delay the onset and decrease the risk of Alzheimer's disease. Prospective studies are needed to establish the dose and duration of **estrogen** required to provide this benefit and to assess its safety in elderly postmenopausal women.

L1 ANSWER 198 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:453766 CAPLUS
DOCUMENT NUMBER: 125:111427
TITLE: Molecular basis of Alzheimer's disease
AUTHOR(S): Gooch, Michael D.; Stennett, Douglass J.
CORPORATE SOURCE: Children's Hospital, Pitt County Memorial Hospital, Greenville, NC, USA
SOURCE: American Journal of Health-System Pharmacy (1996), 53(13), 1545-1557
CODEN: AHSPEK; ISSN: 1079-2082
PUBLISHER: American Society of Health-System Pharmacists
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 122 refs. Information on the mol. biol. of Alzheimer's disease (AD) pointing to new methods of diagnosis and drug therapies is explored. AD is the most common cause of dementia in the elderly and is characterized by senile plaques and neurofibrillary tangles in the brain and loss of cholinergic neurons in the basal forebrain. The disease has a strong genetic component. A definitive diagnosis can be made only by neuropathol. examn. at autopsy or biopsy; however, the accuracy of diagnosis based on std. neuropsychol. testing and inclusion criteria has improved considerably. Senile plaques consist of a central core of **amyloid** fibrils surrounded by dystrophic axons. The main component of senile plaque **amyloid** is a 39 to 42-amino-acid segment referred to as .beta.-**amyloid**, which is derived from **amyloid** precursor protein (APP). APP exists as multiple isoforms encoded by a single gene on chromosome 21. Factors that may influence APP metab. include activation of phospholipase C, phosphorylation, and the cholinergic system. The microtubule-assocd. protein tau may contribute to the neurofibrillary tangles of AD. One of the most important discoveries in AD research was the linking of apolipoprotein E phenotype to familial late-onset AD. Acetylcholinesterase inhibitors appear to improve cognitive function but may be limited in utility by adverse effects. Nicotinic agonists are also being investigated as symptomatic therapies. Other possible strategies include nerve growth factor, agents that potentiate the action of endogenous glutamate, antioxidants, nonsteroidal antiinflammatory drugs, and **estrogens**.

L1 ANSWER 199 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:240785 CAPLUS
DOCUMENT NUMBER: 124:279496
TITLE: **Estrogens** attenuate and corticosterone

exacerbates excitotoxicity, oxidative injury, and **amyloid** .beta.-peptide toxicity in hippocampal neurons

AUTHOR(S): Goodman, Yadong; Bruce, Annadora J.; Cheng, Bin; Mattson, Mark P.

CORPORATE SOURCE: Sanders-Brown Research Center Aging, Univ. Kentucky, Lexington, KY, USA

SOURCE: Journal of Neurochemistry (1996), 66(5), 1836-44
CODEN: JONRA9; ISSN: 0022-3042

PUBLISHER: Lippincott-Raven

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Steroid hormones, particularly **estrogens** and glucocorticoids, may play roles in the pathogenesis of neurodegenerative disorders, but their mechanisms of action are not known. We report that **estrogens** protect cultured hippocampal neurons against glutamate toxicity, glucose deprivation, FeSO4 toxicity, and **amyloid** .beta.-peptide (A.beta.) toxicity. The toxicity of each insult was significantly attenuated in cultures pretreated for 2 h with 100 nM-10 .mu.M 17.beta.-estradiol, estriol, or progesterone. In contrast, corticosterone exacerbated neuronal injury induced by glutamate, FeSO4, and A.beta.. Several other steroids, including testosterone, aldosterone, and vitamin D, had no effect on neuronal vulnerability to the different insults. The protective actions of **estrogens** and progesterone were not blocked by actinomycin D or cycloheximide. Lipid peroxidn. induced by FeSO4 and A.beta. was significantly attenuated in neurons and isolated membranes pretreated with **estrogens** and progesterone, suggesting that these steroids possess antioxidant activities. **Estrogens** and progesterone also attenuated A.beta.- and glutamate-induced elevation of intracellular free Ca2+ concns. We conclude that **estrogens**, progesterone, and corticosterone can directly affect neuronal vulnerability to excitotoxic, metabolic, and oxidative insults, suggesting roles for these steroids in several different neurodegenerative disorders.

L1 ANSWER 200 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:933468 CAPLUS

DOCUMENT NUMBER: 123:330304

TITLE: 17.beta.-Estradiol protects neurons from oxidative stress-induced cell death in vitro

AUTHOR(S): Behl, Christian; Widmann, Martina; Trapp, Thorsten; Holsboer, Florian

CORPORATE SOURCE: Clinical Inst., Max Planck Inst. Psychiatry, Munich, 80804, Germany

SOURCE: Biochemical and Biophysical Research Communications (1995), 216(2), 473-82
CODEN: BBRCA9; ISSN: 0006-291X

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The potential antioxidant activity of 17-.beta. estradiol and other steroid hormones in neuronal cells was investigated by studying oxidative stress-induced cell death caused by the neurotoxins **amyloid** .beta. protein, hydrogen peroxide and glutamate in the clonal mouse hippocampal cell line HT22. Preincubation of the cells with 10-5 M 17-.beta. estradiol prior to addn. of the neurotoxins prevented oxidative stress-induced cell damage and ultimately cell death, as detected with cell viability (MTT) and cell lysis (trypan blue exclusion/cell counting; propidium iodide staining) assays. At the DNA level, 17-.beta. estradiol blocked the DNA degrdn. caused by glutamate. Other steroid hormones, such as progesterone, aldosterone, corticosterone and the steroid precursor cholesterol, did not protect the cells. The neuronal protection afforded

by 17-.beta. estradiol was **estrogen** receptor-independent. These data demonstrate a potent neuroprotective activity of the antioxidant 17-.beta. estradiol, which may have implications for the prevention and treatment of Alzheimer's disease.

L1 ANSWER 201 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:672516 CAPLUS
DOCUMENT NUMBER: 121:272516
TITLE: The effects of aging and hormonal manipulation on **amyloid** precursor protein APP695 mRNA expression in the rat hippocampus
AUTHOR(S): Chao, Helen M.; Spencer, Robert L.; Frankfurt, Maya; McEwen, Bruce S.
CORPORATE SOURCE: Lab. Neuroendocrinology, Rockefeller Univ., New York, NY, 10021, USA
SOURCE: Journal of Neuroendocrinology (1994), 6(5), 517-21
CODEN: JOUNE2; ISSN: 0953-8194
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the rat hippocampus, neuronal morphol. and survival are profoundly affected by adrenal steroids, and synaptic plasticity can be modulated by the ovarian sex steroids **estrogen** and progesterone. .beta.-**Amyloid** peptides, which accumulate in neuritic plaques and are derived from the **amyloid** precursor protein (APP), have been shown to be both trophic and toxic for hippocampal neurons. Of the various APP isoforms, APP695 is the predominant form found in rat brain and the APP695 mRNA is abundantly expressed in the hippocampus. To investigate the hypothesis that APP may serve as a mediator of the steroid effects, the authors have monitored the hippocampal expression of APP695 mRNA by in situ hybridization, with aging and with steroid manipulation. In aged female rats the authors obsd. a decrease in the level of APP695 mRNA relative to young female rats, while no such age difference was evident in male rats. Physiol., surgical and pharmacol. manipulation of glucocorticoids appeared to have no effect on APP695 mRNA levels in the hippocampus. Treatment of young, ovariectomized female rats with **estrogen** and progesterone, resulted in an increase in hippocampal APP695 expression compared to untreated, ovariectomized controls.

L1 ANSWER 202 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:316136 CAPLUS
DOCUMENT NUMBER: 120:316136
TITLE: **Estrogen** regulates metabolism of Alzheimer **amyloid** .beta. precursor protein
AUTHOR(S): Jaffe, Ari B.; Toran-Allerand, C. Dominique; Greengard, Paul; Gandy, Samuel E.
CORPORATE SOURCE: Med. Coll., Cornell Univ., New York, NY, 10021, USA
SOURCE: Journal of Biological Chemistry (1994), 269(18), 13065-8
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors have investigated the possible effect of **estrogen** on the metab. of the Alzheimer **amyloid** precursor protein (APP). Using a cell line that contains high levels of **estrogen** receptors, the authors have found that treatment with physiol. concns. of 17.beta.-estradiol is assocd. with accumulation in the conditioned medium of an amino-terminal cleavage product of APP (sol. APP or protease nexin-2), indicative of non-amyloidogenic processing. There were no obvious changes in the levels of intracellular immature or mature APP holoproteins, suggesting that **estrogen** may increase the secretory metab. of APP.

L1 ANSWER 203 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:264491 CAPLUS
DOCUMENT NUMBER: 120:264491
TITLE: Prediction of the active sites of proteins from amino acid sequences
AUTHOR(S): Numao, Naganori; Kidokoro, Shunichi
CORPORATE SOURCE: Sagami Chem. Res. Cent., Sagamihara, 229, Japan
SOURCE: Biological & Pharmaceutical Bulletin (1993), 16(11), 1160-3
CODEN: BPBLEO; ISSN: 0918-6158
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The discriminant anal. of complementary units and repeated sequences of amino acids in an initial sample of 48 different enzymes produces practically useful empirical-function which allow catalytic sites to be distinguished from non-catalytic sites. The independent variables in the discrimination functions were almost all composed of complementary units of amino acids, that is amino acid sequences whose nucleotide coding sequences were complementary to each other. In order of evaluate the validity of the functions, the authors applied them to the amino acid sequences of 17 different kinds of enzymes as well as 30 non-enzymes such as receptors, oncoproteins, cytokines, hormones and so on. The functions proved to be effective in predicting not only the catalytic sites of enzymes but also the binding sites of the other proteins. The results that complementary units are evolutionarily conserved as a signal around the active sites of various proteins.

L1 ANSWER 204 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1993:642363 CAPLUS
DOCUMENT NUMBER: 119:242363
TITLE: Serum **amyloid** P (female protein) of the Syrian hamster. Gene structure and expression
AUTHOR(S): Rudnick, Caroline M.; Dowton, S. Bruce
CORPORATE SOURCE: Sch. Med., Washington Univ., St. Louis, MO, 63110, USA
SOURCE: Journal of Biological Chemistry (1993), 268(29), 21760-9
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The structure and expression of the gene encoding serum **amyloid** P (SAP) component of the Syrian hamster have been studied by isolation of cosmid clones, nucleotide sequence analyses, and quantitation of nuclear run-on transcripts, nuclear RNA, mRNA, and protein levels. Hamster SAP, originally identified as female protein (FP), is a unique pentraxin because pretranslational expression of this gene is modulated by mediators of inflammation and sex steroids. SAP(FP) levels are high in sera from female hamsters and low in males. The response to inflammation is divergent; SAP(FP) levels decrease in females and increase in males during an acute phase response. The SAP(FP) gene encodes a 211-amino acid residue mature polypeptide as well as a 22-residue signal peptide. The intron/exon organization is similar to that of other pentraxins, but addnl. transcripts are generated from alternate polyadenylation sites in the 3' region. Circulating levels of SAP (FP) and the corresponding hepatic transcript levels are augmented by **estrogen**, whereas testosterone, dexamethasone, and progesterone cause a decrease in these levels. In addn. the cytokines interleukin-1, -6, and tumor necrosis factor mediate a decrease in hepatic SAP(FP) transcript levels in female hamsters but did not cause a significant elevation of SAP(FP) mRNA in livers of male hamsters. The differences in expression of the SAP(FP) gene between male and female hamsters and between unstimulated male hamsters and male hamsters stimulated with an injection of

lipopolysaccharide are due, at least in part, to alterations in transcription.

L1 ANSWER 205 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:229405 CAPLUS
DOCUMENT NUMBER: 116:229405
TITLE: A genetic linkage map of human chromosome 21: analysis of recombination as a function of sex and age
AUTHOR(S): Tanzi, Rudolph E.; Watkins, Paul C.; Stewart, Gordon D.; Wexler, Nancy S.; Gusella, James F.; Haines, Jonathan L.
CORPORATE SOURCE: Mol. Neurogenet. Lab., Massachusetts Gen. Hosp., Boston, MA, USA
SOURCE: American Journal of Human Genetics (1992), 50(3), 551-8
CODEN: AJHGAG; ISSN: 0002-9297
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A genetic linkage map of human chromosome 21 has been constructed using 22 anonymous DNA markers and five cDNAs (cDNAs) encoding the **amyloid** .beta. protein precursor (APP), superoxide dismutase 1 (SOD1), the etx-2 proto-oncogene (ETS2), the **estrogen** inducible breast cancer locus ((BCE)) and the leukocyte antigen, CD18 (CD18). Segregation of RFLPs detected by these DNA markers was traced in the Venezuelan Ref. Pedigree (VRP). A comprehensive genetic linkage map consisting of the 27 DNA markers span 102 cM on the long arm of chromosome 21. Initial findings were confirmed of a dramatically increased rate of recombination at the telomere in both females and males and of significantly higher recombinations in females in the pericentromeric region. By comparing patterns of recombination in specific regions of chromosome 21 with regard to both parental sex and age, a statistically significant downward trend was identified in the frequency of crossovers in the most telomeric portion of chromosome 21 with increasing maternal age. A less significant decrease in recombination with increasing maternal age was obsd. in the pericentromeric region of the chromosome. These results may help in ultimately understanding the phys. relationship between recombination and nondisjunction in the occurrence of trisomy 21.

L1 ANSWER 206 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:192015 CAPLUS
DOCUMENT NUMBER: 116:192015
TITLE: Down syndrome: molecular mapping of the congenital heart disease and duodenal stenosis
AUTHOR(S): Korenberg, J. R.; Bradley, C.; Disteche, C. M.
CORPORATE SOURCE: Ahmanson Dep. Pediatr., Univ. California, Los Angeles, CA, USA
SOURCE: American Journal of Human Genetics (1992), 50(2), 294-302
CODEN: AJHGAG; ISSN: 0002-9297
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Down syndrome (DS) is a major cause of congenital heart and gut disease and mental retardation. DS individuals also have characteristic facies, hands, and dermatoglyphics, in addn. to abnormalities of the immune system, an increased risk of leukemia, and an Alzheimer-like dementia. Although the mol. basis of these features is unknown, recent work on patients with DS and partial duplications of chromosome 21 has suggested small chromosomal regions located in band q22 that are likely to contain the genes for some of these features. Here, these analyses are extended to define mol. markers for the congenital heart disease, the duodenal stenosis, and an "overlap" region for the facial and some of the skeletal features. The clin., cytogenetic, and mol. analyses of two patients are

reported. The first is DUP21JS, which carries both a partial duplication of chromosome 21, including the region 21q21.1-q22.13, or proximal q22.2, and DS features including duodenal stenosis. Using quant. Southern blot dosage anal. and 15 DNA sequences unique to chromosome 21, the mol. extent of the duplication was defined. This includes the region defined by DNA sequences for APP (**amyloid** precursor protein), SOD1 (CuZn superoxide dismutase), D21S47, SF57, D21S17, D21S55, D21S3, and D21S15 and excludes the regions defined by DNA sequences for D21S16, D21S46, D21S1, D21S19, BCE I (breat cancer **estrogen**-inducible gene), D21S39, and D21S44. Using similar techniques, the region duplicated in the second case occurring in a family carrying a translocation assocd. with DS and congenital heart disease was also defined. This region includes DNA sequences for D21S55 and D21S3 and excludes DNA sequences for D21S47 and D21S17. The DS mol.-overlap region is defined by the three DNA sequences duplicated in both patients and includes D21S55, D21S3, and D21S15. These studies provide the mol. basis for the construction of a DS phenotypic map and focus the search for genes responsible for the phys. features, congenital heart disease, and duodenal stenosis of DS.

L1 ANSWER 207 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:167598 CAPLUS
DOCUMENT NUMBER: 116:167598
TITLE: Detailed genetic linkage map of human chromosome 21: patterns of recombination according to age and sex
AUTHOR(S): Tanzi, Rudolph E.; Haines, Jonathan L.; Gusella, James F.
CORPORATE SOURCE: Mol. Neurogenet. Lab., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SOURCE: Progress in Clinical and Biological Research (1990), 360(Mol. Genet. Chromosome 21 Down Syndr.), 15-26
CODEN: PCBRD2; ISSN: 0361-7742
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To more precisely localize the genes responsible for familial Alzheimer's disease and Down syndrome, the authors have constructed a detailed genetic linkage map of chromosome 21 consisting of 21 anonymous DNA markers and five genes (**amyloid** protein precursor [APP], superoxide dismutase 1 [SOD1], the ets-2 protooncogene [ETS2], the **estrogen** inducible breast cancer locus [BCEI], and the leukocyte antigen, CD18 [CD18]). The map spans a total of 76 centimorgans (cM) with the markers D21S16 and CD18 representing the proximal and distal endpoints, resp. Previously the authors reported a dramatically increased rate of recombination for both male and female meioses near the telomere, particularly in the distal portion of band 21q22.3 (R. E. Tanzi et al., 1988). In addn., they reported that the frequency of crossovers is statistically higher in females in the peri-centromeric region of 21q between the markers D21S1/S11 and D21S13/S16. The more detailed genetic linkage map confirmed these previous observations on the patterns of recombination for chromosome 21, and addnl. differences in behavior of the chromosome based on both parental sex and age are presented. A significant decrease in recombination with increased parental age near the telomere, a less significant decrease in the subcentromeric region, and a trend toward decreasing nos. of double crossover events with increasing parental age was obsd. The possible significance of these findings with regard to nondisjunction will be discussed.

L1 ANSWER 208 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:405853 CAPLUS
DOCUMENT NUMBER: 115:5853
TITLE: Changes in 40 serum proteins of post-menopausal women
AUTHOR(S): Hashimoto, Shigeru; Miwa, Masahiko; Akasofu, Kazutomo; Nishida, Etsuro

CORPORATE SOURCE: Sch. Med., Kanazawa Univ., Kanazawa, 920, Japan
SOURCE: Maturitas (1991), 13(1), 23-33
CODEN: MATUDK; ISSN: 0378-5122
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Sera were sampled from pre- and post-menopausal women and men. Climacteric symptoms of women were treated with conjugated **estrogen**. Sera were sampled serially until the 21st day of **estrogen** administration. Serum concns. of 40 protein components were measured by micro single radial immunodiffusion. The serum proteins were classified into 5 types according to changes after menopause and **estrogen** therapy. Type 1 (decreased after menopause and increased by **estrogen**; .alpha.1-antitrypsin, .alpha.2-HS-glycoprotein, .beta.2-glycoprotein III, Gc-globulin, .alpha.1-lipoprotein, and .alpha.2-AP-glycoprotein), type 2 (unchanged and increased; ceruloplasmin), type 3 (increased and decreased; .alpha.1-acid glycoprotein, haptoglobin, serum **amyloid** P-component, Zn-.alpha.2-glycoprotein, .beta.-lipoprotein, and C1-components), type 4 (unchanged and decreased; hemopexin, antithrombin III, .beta.2-glycoprotein I, prealbumin, and retinol-binding protein), type 5 (unchanged by **estrogen**; IgM, IgG, and others). **Estrogen** replacement therapy restored pre-menopausal levels of serum proteins, types 1 and 3. However, **estrogen** therapy was assocd. with significantly abnormal levels of proteins, types 2 and 4 in post-menopausal women. Serum levels of type 1 proteins and some type 5 proteins (IgM, .alpha.1B-glycoprotein, C9-component, and .alpha.2-macroglobulin) were higher in pre-menopausal women than in men, whereas type 3 proteins were the opposite.

L1 ANSWER 209 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:526740 CAPLUS
DOCUMENT NUMBER: 113:126740
TITLE: Armenian hamster female protein: a pentraxin under complex regulation
AUTHOR(S): Coe, John E.; Ross, Mary Jane
CORPORATE SOURCE: Lab. Persistent Viral Dis., Natl. Inst. Allergy Infect. Dis., Hamilton, MT, 59840, USA
SOURCE: American Journal of Physiology (1990), 259(2, Pt. 2), R341-R349
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The serum of Armenian hamster (Cricetulus migratorius) contains a protein homologous to female protein (FP) that has been characterized in the Syrian (golden) hamster. Of unknown function, FP belongs to a family of proteins (called pentraxins) that have a common ancestral gene and are widely expressed in nature. Whereas serum concn. of FP in Syrian hamsters (SFP) is many fold greater (200-300-fold) in females vs. males, Armenian hamster FP (AFP) is only moderately elevated (.apprx.3-fold) in female vs. males and only for the fall-winter mos of the yr. In the Armenian hamster, testosterone administration to females or castration of males has no effect on AFP serum levels; in Syrian hamster, these treatments change SFP serum concn. to that characteristic of the opposite sex. Some sex steroid content of hepatic AFP synthesis is evident, however, as serum levels decrease after exogenous **estrogen** treatment. In contrast to Syrian hamster FP, normal levels of AFP are more dependent on an intact pituitary and also are influenced by the season of the year. As an acute-phase protein, AFP responds in a typical fashion, with increasing serum levels detected in both sexes in contrast to the divergent sex-limited response in Syrian hamsters. Although AFP and SFP are similar structurally, morphol., and antigenetically and share common binding specificities, the regulation of FP synthesis in Armenian hamster is very

different from that previously found in Syrian hamster.

L1 ANSWER 210 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:233511 CAPLUS
DOCUMENT NUMBER: 112:233511
TITLE: Amyloidosis and female protein in the Syrian hamster. Concurrent regulation by sex hormones
AUTHOR(S): Coe, John E.; Ross, Mary Jane
CORPORATE SOURCE: Natl. Inst. Allergy Infect. Dis., Lab. Persistent Viral Dis., Hamilton, MT, 59840, USA
SOURCE: Journal of Experimental Medicine (1990), 171(4), 1257-67
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The influence of testosterone (I) on the expression of **amyloid** was tested to det. if this hormone is solely responsible for the sex-limited amyloidosis of the Syrian hamster (Mesocricetus auratus). Males deprived of I by castration acquired **amyloid** at an unusually young age, an age of onset similar to that in female hamsters. Also, the amyloidogenic effect of DES in male Syrian hamster was inhibited by concomitant injections of I, indicating that **estrogens** induce **amyloid** in male hamsters by inhibiting I synthesis. When administered to female hamsters, I inhibited expression of **amyloid** in aging female Syrian hamsters and extended the life span of this gender. Of the 2 components of **amyloid**, the major component **Amyloid** A-derived fibril or the minor constituent **Amyloid** P component, only the P component is under sex hormone control in the Syrian hamster; I inhibits the hepatic synthesis of the P component homolog (called female protein), which is normally expressed 100-200-fold greater in female vs. male Syrian hamsters. In general, the serum level of the female protein under various exptl. conditions correlated with the presence of **amyloid** and indicated that in the Syrian hamster the P component homolog is of primary importance in the deposition of **amyloid**.

L1 ANSWER 211 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1966:493290 CAPLUS
DOCUMENT NUMBER: 65:93290
ORIGINAL REFERENCE NO.: 65:17487b-c
TITLE: Amyloidosis in **estrogen** and carcinogen-treated mice
AUTHOR(S): Boonyanit, Soonthorn
CORPORATE SOURCE: Univ. of Kansas Med. Center, Kansas City
SOURCE: Archives of Pathology (1966), 82(4), 379-83
CODEN: ARPAAQ; ISSN: 0363-0153
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Amyloidosis was found in **estrogen**-treated, castrated female Call mice during a study on exptl. carcinogenesis of the uterine cervix. The incidence and severity of amyloidosis was increased when the subcutaneous .beta.-estradiol or estriol injections were given concomitantly with topical applications of 3,4-benzopyrene to the cervix. The organ distribution of **amyloid** was similar to that after injections of sol. antigens. Various cellular changes, considered to be degenerative, were assocd. with the **estrogen** injections. The increased **amyloid** incidence suggests a synergistic effect between these agents. 31 references.

L1 ANSWER 212 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1950:8103 CAPLUS
DOCUMENT NUMBER: 44:8103

ORIGINAL REFERENCE NO.: 44:1595b-g
TITLE: Constitutional factors in resistance to infection. I. The effect of **estrogen** and chorionic gonadotropin on the course of tuberculosis in highlyinbred rabbits. II. The effect of **estrogen** on tuberculin skin sensitivity and on the allergy of the internal tissues. III. Action of **estrogen** and gonadotropin on the progress of tuberculosis
AUTHOR(S): Lurie, Max B.; Abramson, Samuel; Allison, Marvin J.; Harris, T. N.; Heppleston, A. G.
SOURCE: American Review of Tuberculosis (1949), 59, 168-85,186-97,198-218
CODEN: ARTUA4; ISSN: 0096-0381
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB In highly inbred, sexually mature rabbits **estrogen** in large doses retarded the disease at the site of intracutaneous inoculation, diminished the extent of the internal disease, and suppressed dissemination. In immature rabbits it was less effective on the spread of the disease. In highly inbred rabbits periodic administration of chorionic gonadotropin, which induced ovarian corpora lutea in the earlier phase of the disease, enhanced progress of the disease at the site of injection, increased dissemination, and aggravated internal disease. Ovariectomy or daily combined injection of physiol. amts. of progesterone and estradiol had no effect. **Estrogen** reduced the inflammatory skin response to tuberculin in rabbits sensitized by active tuberculosis or by treatment with heat-killed tubercle bacilli, by virtue of the depressing effect of the hormone on the inflammatory irritability of the skin to bacterial irritants in general. Acquisition of intrinsic allergic sensitivity of the tissues in general, as well as that of the skin, was not reduced by **estrogen** administration. **Estrogen** retarded the progress of tuberculosis in the skin and diminished its internal dissemination chiefly by reducing permeability of connective tissue. Chorionic gonadotropin enhanced the disease at the portal of entry and its spread through the body by increasing permeability of the connective tissue. Hyaluronidase exerted a greater spreading effect in **estrogen**-treated animals than in those treated with gonadotropin. **Estrogen** reduced the no. of circulating lymphocytes. Intermediation of the adrenal cortex in this effect was not shown. Tuberculosis induces a marked adrenal hypertropy in rabbits. Reduction of the inflammatory responsiveness of the skin to the products of tubercle bacilli induced by **estrogen** is not a significant factor in its capacity to retard the tuberculous process. **Estrogen** and gonadotropin exert no effect on antibody formation. **Estrogen**

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| NEWS 13 | DEC 09 | STN Entry Date available for display in REGISTRY and CA/CAplus |
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| NEWS 20 | JAN 27 | Source of Registration (SR) information in REGISTRY updated and searchable |
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| NEWS EXPRESS | DECEMBER 28 CURRENT WINDOWS VERSION IS V7.00, CURRENT MACINTOSH VERSION IS V6.0b(ENG) AND V6.0Jb(JP), AND CURRENT DISCOVER FILE IS DATED 23 SEPTEMBER 2003 |
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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.84       0.84

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FILE COVERS 1907 - 29 Jan 2004  VOL 140 ISS 5
FILE LAST UPDATED: 28 Jan 2004  (20040128/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s estrogen and amyloid
         65804 ESTROGEN
         46669 ESTROGENS
         77046 ESTROGEN
                 (ESTROGEN OR ESTROGENS)
         17307 AMYLOID
          1587 AMYLOIDS
         17389 AMYLOID
                 (AMYLOID OR AMYLOIDS)
L1         212 ESTROGEN AND AMYLOID

=> s 1 and estradiol
       7789321 1
         69513 ESTRADIOL
           347 ESTRADIOLS
         69599 ESTRADIOL
                 (ESTRADIOL OR ESTRADIOLS)
L2       30175 1 AND ESTRADIOL

=> s L1 and estradiol
         69513 ESTRADIOL
           347 ESTRADIOLS
         69599 ESTRADIOL
                 (ESTRADIOL OR ESTRADIOLS)
L3          86 L1 AND ESTRADIOL

=> s L3 and equine
          8400 EQUINE
           120 EQUINES
          8470 EQUINE
```

(EQUINE OR EQUINES)
L4 1 L3 AND EQUINE

=> d L4 ibib abs hitrn

L4 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:973165 CAPLUS
TITLE: A comparison of the anti-inflammatory activities of conjugated **estrogens** and 17-.beta. **estradiol**
AUTHOR(S): Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.; Bryant, M.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, 33612-4799, USA
SOURCE: Inflammation Research (2003), 52(11), 452-460
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Unregulated chronic inflammatory process partly due to an **estrogen** deficiency may render postmenopausal women vulnerable to degenerative conditions such as arthritis, osteoporosis, atherosclerosis, and Alzheimer's disease. Current confusion regarding therapeutic efficacy of **estrogen** replacement therapy may be due to different **estrogen** formulations used, short term therapy, as well as advanced stage of the disease. We compared anti-inflammatory activities of two major **estrogen** prepns., conjugated **equine** **estrogen** (CEE) and 17-.beta. **estradiol**, using an animal model (rat mesentery) of in vivo inflammatory reaction to i.v. infused **amyloid**-.beta., examd. by video recording and subsequently analyzed by transmission electron microscopy. Cellular markers of inflammation were monitored: leukocyte migration, platelet activation, mast cell activation/degranulation, and endothelial disruption. Low doses of CEE (0.3 mg/kg for 3 wk) demonstrated significant anti-inflammatory activity, whereas even at high doses (2.0 mg) 17-.beta. **estradiol** had only minimal activity. CEE, a mixt. of several compds., may have some component(s) with significant anti-inflammatory activity. The anti-inflammatory activity of CEE may have a role in prevention of several degenerative diseases assocd. with menopause.

=> s L1 and equine
8400 EQUINE
120 EQUINES
8470 EQUINE
(EQUINE OR EQUINES)
L5 5 L1 AND EQUINE

=> d L5 1-5 ibib abs hitrn

L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:973165 CAPLUS
TITLE: A comparison of the anti-inflammatory activities of conjugated **estrogens** and 17-.beta. estradiol
AUTHOR(S): Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.; Bryant, M.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, 33612-4799, USA
SOURCE: Inflammation Research (2003), 52(11), 452-460
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Unregulated chronic inflammatory process partly due to an **estrogen** deficiency may render postmenopausal women vulnerable to degenerative conditions such as arthritis, osteoporosis, atherosclerosis, and Alzheimer's disease. Current confusion regarding therapeutic efficacy of **estrogen** replacement therapy may be due to different **estrogen** formulations used, short term therapy, as well as advanced stage of the disease. We compared anti-inflammatory activities of two major **estrogen** prepns., conjugated **equine estrogen** (CEE) and 17-.beta. estradiol, using an animal model (rat mesentery) of in vivo inflammatory reaction to i.v. infused **amyloid**-.beta., examd. by video recording and subsequently analyzed by transmission electron microscopy. Cellular markers of inflammation were monitored: leukocyte migration, platelet activation, mast cell activation/degranulation, and endothelial disruption. Low doses of CEE (0.3 mg/kg for 3 wk) demonstrated significant anti-inflammatory activity, whereas even at high doses (2.0 mg) 17-.beta. estradiol had only minimal activity. CEE, a mixt. of several compds., may have some component(s) with significant anti-inflammatory activity. The anti-inflammatory activity of CEE may have a role in prevention of several degenerative diseases assocd. with menopause.

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:575349 CAPLUS

DOCUMENT NUMBER: 139:317654

TITLE: An **estrogen** replacement therapy containing nine synthetic plant-based conjugated **estrogens** promotes neuronal survival

AUTHOR(S): Zhao, Lixia; Chen, Shuhua; Brinton, Roberta D.

CORPORATE SOURCE: Department of Molecular Pharmacology & Toxicology and Neuroscience Program, Pharmaceutical Sciences Center, University of Southern California, Los Angeles, CA, 90089, USA

SOURCE: Experimental Biology and Medicine (Maywood, NJ, United States) (2003), 228(7), 823-835
CODEN: EBMMBE; ISSN: 1535-3702

PUBLISHER: Society for Experimental Biology and Medicine

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Epidemiol. data from retrospective and case-control studies have indicated that **estrogen** replacement therapy can decrease the risk of developing Alzheimer's disease. In addn., **estrogen** replacement therapy has been found to promote neuronal survival both in vivo and in vitro. We have shown that conjugated **equine estrogens** (CEE), contg. 238 different mols. composed of **estrogens**, progestins, and androgens, exerted neurotrophic and neuroprotective effects in cultured neurons. In the current study, we sought to det. whether a steroidal formulation of nine synthetic conjugated **estrogens** (SCE) chem. derived from soybean and yam exts. is as effective as the complex multi-steroidal formulation of CEE. Analyses of the neuroprotective efficacy indicate that SCE exhibited significant neuroprotection against beta **amyloid**, hydrogen peroxide, and glutamate-induced toxicity in cultured hippocampal neurons. Indexes of neuroprotection included an increase in neuronal survival, a decrease in neurotoxin-induced lactate dehydrogenase release, and a redn. in neurotoxin-induced apoptotic cell death. Furthermore, SCE was found to attenuate excitotoxic glutamate-induced [Ca2+]i rise. Quant. analyses indicate that the neuroprotective efficacy of SCE was comparable to that of the multi-steroidal CEE formulation. Data derived from these investigations predict that SCE could exert neuroprotective effects comparable to CEE in vivo and therefore could reduce the risk of Alzheimer's disease in post-menopausal women.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:933950 CAPLUS
DOCUMENT NUMBER: 138:202924
TITLE: Animal model of **amyloid**-.beta. induced vascular inflammation and prevention by **estrogen** and other agents
AUTHOR(S): Rhodin, J.; Thomas, T.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, USA
SOURCE: World Congress for Microcirculation, submitted Papers, 7th, Sydney, Australia, Aug. 19-22, 2001 (2001), 543-547. Monduzzi Editore: Bologna, Italy.
CODEN: 69DILJ; ISBN: 88-323-1819-9
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Inflammatory processes play a prominent role in the pathol. of a no. of diseases ranging from arthritis, atherosclerosis, cancer and Alzheimer's disease. Utilizing a live animal (rat) model, and combining intravital video recordings of mesenteric microvascular bed with TEM analyses of the same vascular segments, the authors demonstrate inflammatory responses by arterioles and venules after infusion of **amyloid**-.beta.(1-40), the protein accumulating in brains of Alzheimer patients. The inflammatory responses were prevented by administering the following agents before the **amyloid**: (A) superoxide dismutase; (B) tumor necrosis factor-binding protein; (C) interleukin-1 receptor antagonist; (D) conjugated **equine estrogen**; (E) RAGE antibody.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:348873 CAPLUS
DOCUMENT NUMBER: 136:380367
TITLE: Effect of medroxyprogesterone acetate on vascular inflammatory markers in postmenopausal women receiving **estrogen**
AUTHOR(S): Wakatsuki, Akihiko; Okatani, Yuji; Ikenoue, Nobuo; Fukaya, Takao
CORPORATE SOURCE: Department of Obstetrics and Gynecology, Kochi Medical School, Nankoku, Kochi, 783-8505, Japan
SOURCE: Circulation (2002), 105(12), 1436-1439
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Estrogen** increases C-reactive protein (CRP) in postmenopausal women. **Estrogen** also decreases cell adhesion mols., whereas elevated CRP stimulates the expression of cell adhesion mols. Because androgens have antiinflammatory effects, androgenic progestins such as medroxyprogesterone acetate (MPA) may inhibit proinflammatory effects of **estrogen**. We investigated the effects of MPA on **estrogen** -induced changes in acute inflammatory proteins and cell adhesion mols. in postmenopausal women. Postmenopausal women were treated daily with conjugated **equine estrogen** (CEE, 0.625 mg), CEE plus MPA 2.5 mg, or CEE plus MPA 5.0 mg for 3 mo. CEE significantly increased CRP concns. by 320.1.+-.210.2% ($P<0.05$). The addn. of MPA to CEE, however, inhibited the increase in CRP in a concn.-dependent manner (MPA 2.5 mg, 169.8.+-.66.9%, $P<0.05$; MPA 5 mg, 55.0.+-.30.4%, not significant). Similarly, CEE increased **amyloid** A protein concns., whereas MPA reversed this effect. Interleukin-6 concn. did not change significantly

in any treatment group. CEE alone significantly decreased the concn. of E-selectin, but the concns. of intercellular adhesion mol. and vascular cellular adhesion mol. did not change significantly. The addn. of MPA tended to decrease the levels of cell adhesion mols., and use of 5.0 mg MPA showed significant decreases in all cell-adhesion mol. concns. Concurrent MPA administration may attenuate **estrogen**'s proinflammatory effect. Because MPA in combination with CEE decreased cell adhesion mol. concns., the anti-inflammatory effect of MPA may actually be responsible for the favorable effect of **estrogen** -progestogen combinations on cell adhesion mols. in postmenopausal women.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:366985 CAPLUS

DOCUMENT NUMBER: 133:99758

TITLE: The **estrogen** replacement therapy of the Women's Health Initiative promotes the cellular mechanisms of memory and neuronal survival in neurons vulnerable to Alzheimer's disease

AUTHOR(S): Brinton, Roberta Diaz; Chen, Shuhua; Montoya, Marissa; Hsieh, Debra; Minaya, Jasmin

CORPORATE SOURCE: Department of Molecular Pharmacology and Toxicology and the Program in Neuroscience, Pharmaceutical Sciences Center, USC STAR Program, University of Southern California, Los Angeles, CA, 90033, USA

SOURCE: Maturitas (2000), 34(Suppl. 2), S35-S52
CODEN: MATUDK; ISSN: 0378-5122

PUBLISHER: Elsevier Science Ireland Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The current study investigated the neurotrophic and neuroprotective action of the complex formulation of conjugated **equine** **estrogens** (CEEs), the most frequently prescribed **estrogen** replacement therapy in the United States and the **estrogen** replacement therapy of the Women's Health Initiative. Videomicroscopic, morphol. and biochem. analyses were conducted in primary cultures of hippocampal neurons to det. the neurotrophic and neuroprotective properties of CEEs. Results of these analyses demonstrated that CEEs significantly increased hippocampal neuronal outgrowth, a cellular marker of memory formation. Dose response analyses indicated that the lowest effective concn. of CEEs exerted the maximal neurotrophic effect. Of neuroprotection studies demonstrated that CEES induced highly significant neuroprotection against beta amyloid25-35, hydrogen peroxide and glutamate-induced toxicity. CEEs induced cellular markers of memory function in neurons crit. to memory and vulnerable to neg. effects of aging and Alzheimer's disease. In addn., CEEs significantly and potently protected neurons against toxic insults assocd. with Alzheimer's disease. Because CEEs are the **estrogen** replacement therapy of the Women's Health Initiative, results of the current study could provide cellular mechanisms for effects of CEEs on cognitive function and risk of Alzheimer's disease derived from this prospective clin. trial.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s estrogen and amyloid beta
65804 ESTROGEN
46669 ESTROGENS
77046 ESTROGEN
(ESTROGEN OR ESTROGENS)
17307 AMYLOID

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          1587 AMYLOIDS
         17389 AMYLOID
                 (AMYLOID OR AMYLOIDS)
       1234929 BETA
          1326 BETAS
       1234995 BETA
                 (BETA OR BETAS)
          6387 AMYLOID BETA
                 (AMYLOID(W)BETA)
L6         105 ESTROGEN AND AMYLOID BETA

=> s L6 and equine
          8400 EQUINE
           120 EQUINES
          8470 EQUINE
                 (EQUINE OR EQUINES)
L7           3 L6 AND EQUINE

=> d L7 1-3 ibib abs hitrn

L7   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2003:973165  CAPLUS
TITLE:                   A comparison of the anti-inflammatory activities of
                         conjugated estrogens and 17-.beta. estradiol
AUTHOR(S):               Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.;
                         Bryant, M.
CORPORATE SOURCE:        Department of Anatomy, College of Medicine, University
                         of South Florida, Tampa, FL, 33612-4799, USA
SOURCE:                  Inflammation Research (2003), 52(11), 452-460
                         CODEN: INREFB; ISSN: 1023-3830
PUBLISHER:               Birkhaeuser Verlag
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Unregulated chronic inflammatory process partly due to an estrogen
     deficiency may render postmenopausal women vulnerable to degenerative
     conditions such as arthritis, osteoporosis, atherosclerosis, and
     Alzheimer's disease.  Current confusion regarding therapeutic efficacy of
     estrogen replacement therapy may be due to different
     estrogen formulations used, short term therapy, as well as
     advanced stage of the disease.  We compared anti-inflammatory activities
     of two major estrogen prepns., conjugated equine
     estrogen (CEE) and 17-.beta. estradiol, using an animal model (rat
     mesentery) of in vivo inflammatory reaction to i.v. infused
     amyloid-.beta., examd. by video recording and
     subsequently analyzed by transmission electron microscopy.  Cellular
     markers of inflammation were monitored: leukocyte migration, platelet
     activation, mast cell activation/degranulation, and endothelial
     disruption.  Low doses of CEE (0.3 mg/kg for 3 wk) demonstrated
     significant anti-inflammatory activity, whereas even at high doses (2.0
     mg) 17-.beta. estradiol had only minimal activity.  CEE, a mixt. of
     several compds., may have some component(s) with significant
     anti-inflammatory activity.  The anti-inflammatory activity of CEE may
     have a role in prevention of several degenerative diseases assocd. with
     menopause.

L7   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:        2002:933950  CAPLUS
DOCUMENT NUMBER:         138:202924
TITLE:                   Animal model of amyloid-.beta.
                         induced vascular inflammation and prevention by
                         estrogen and other agents
AUTHOR(S):               Rhodin, J.; Thomas, T.
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CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, USA
SOURCE: World Congress for Microcirculation, submitted Papers, 7th, Sydney, Australia, Aug. 19-22, 2001 (2001), 543-547. Monduzzi Editore: Bologna, Italy.
CODEN: 69DILJ; ISBN: 88-323-1819-9
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Inflammatory processes play a prominent role in the pathol. of a no. of diseases ranging from arthritis, atherosclerosis, cancer and Alzheimer's disease. Utilizing a live animal (rat) model, and combining intravital video recordings of mesenteric microvascular bed with TEM analyses of the same vascular segments, the authors demonstrate inflammatory responses by arterioles and venules after infusion of **amyloid-.beta**.(1-40), the protein accumulating in brains of Alzheimer patients. The inflammatory responses were prevented by administering the following agents before the amyloid: (A) superoxide dismutase; (B) tumor necrosis factor-binding protein; (C) interleukin-1 receptor antagonist; (D) conjugated **equine estrogen**; (E) RAGE antibody.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:366985 CAPLUS
DOCUMENT NUMBER: 133:99758
TITLE: The **estrogen** replacement therapy of the Women's Health Initiative promotes the cellular mechanisms of memory and neuronal survival in neurons vulnerable to Alzheimer's disease
AUTHOR(S): Brinton, Roberta Diaz; Chen, Shuhua; Montoya, Marissa; Hsieh, Debra; Minaya, Jasmin
CORPORATE SOURCE: Department of Molecular Pharmacology and Toxicology and the Program in Neuroscience, Pharmaceutical Sciences Center, USC STAR Program, University of Southern California, Los Angeles, CA, 90033, USA
SOURCE: Maturitas (2000), 34(Suppl. 2), S35-S52
CODEN: MATUDK; ISSN: 0378-5122
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The current study investigated the neurotrophic and neuroprotective action of the complex formulation of conjugated **equine estrogens** (CEEs), the most frequently prescribed **estrogen** replacement therapy in the United States and the **estrogen** replacement therapy of the Women's Health Initiative. Videomicroscopic, morphol. and biochem. analyses were conducted in primary cultures of hippocampal neurons to det. the neurotrophic and neuroprotective properties of CEEs. Results of these analyses demonstrated that CEEs significantly increased hippocampal neuronal outgrowth, a cellular marker of memory formation. Dose response analyses indicated that the lowest effective concn. of CEEs exerted the maximal neurotrophic effect. Of neuroprotection studies demonstrated that CEES induced highly significant neuroprotection against beta amyloid25-35, hydrogen peroxide and glutamate-induced toxicity. CEEs induced cellular markers of memory function in neurons crit. to memory and vulnerable to neg. effects of aging and Alzheimer's disease. In addn., CEEs significantly and potently protected neurons against toxic insults assocd. with Alzheimer's disease. Because CEEs are the **estrogen** replacement therapy of the Women's Health Initiative, results of the current study could provide cellular mechanisms for effects of CEEs on cognitive function and risk of Alzheimer's disease derived from this prospective clin. trial.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d L1 1-212 ibib abs hitrn

L1 ANSWER 1 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:68640 CAPLUS
TITLE: Hormone therapy and Alzheimer's disease: benefit or harm?
AUTHOR(S): Henderson, Victor W.
CORPORATE SOURCE: 4301 W Markham Street, Donald W Reynolds Center on Aging, University of Arkansas for Medical Sciences, 810, Little Rock, AR, 72205 USA, USA
SOURCE: Expert Opinion on Pharmacotherapy (2004), 5(2), 389-406
CODEN: EOPHF7; ISSN: 1465-6566
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer's disease (AD) is the most common cause of dementia. After menopause, circulating levels of **estrogens** decline markedly and **estrogen** influences several brain processes predicted to modify AD risk. For example, **estrogen** reduces the formation of .beta.-**amyloid**, a biochem. hallmark of AD. **Estrogen** effects on oxidative stress and some effects on inflammation and the cerebral vasculature might also be expected to ameliorate risk. However, AD pathogenesis is incompletely understood and other **estrogen** actions could be deleterious. Limited clin. trial evidence suggests that **estrogen** therapy, begun after the onset of AD symptoms, is without substantial benefit or harm. Observational studies have assocd. **estrogen**-contg. hormone therapy with reduced AD risk. However, in the Women's Health Initiative Memory Study - a randomised, placebo-controlled trial of women 65 - 79 yr of age - oral **estrogen** plus progestin doubled the rate of dementia, with heightened risk appearing soon after treatment was initiated. Based on current evidence, hormone therapy is thus not indicated for the prevention of AD. Discrepancies between observational studies and the Women's Health Initiative clin. trial may reflect biases and unrecognised confounding factors in observational reports. Other explanations for divergent findings should be considered in future research, including effects of unopposed **estrogen** or different hormone therapy prepns. and the intriguing theor. possibility that effects of hormone therapy on AD risk may be modified by the timing of use (e.g., initiation during the menopausal transition or early postmenopause vs. initiation during the late postmenopause).

L1 ANSWER 2 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:20807 CAPLUS
TITLE: Use of peptides derived from junctional adhesion molecules to permeabilize mucosa for improved efficiency of mucosal delivery of therapeutic compounds
INVENTOR(S): Quay, Steven C.
PATENT ASSIGNEE(S): Nastech Pharmaceutical Company, Inc., USA
SOURCE: PCT Int. Appl., 426 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
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| WO 2004003145 | A2 | 20040108 | WO 2003-US19994 | 20030624 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-392512P P 20020628

AB Methods of improving the permeability of mucosal epithelia to improve the efficiency of transmucosal delivery of drugs are described. Permeability is improved by modulating epithelial junction structure or physiol. of the mucosa using a peptide derived from one of the proteins involved in the junction, such as junctional adhesion mols. (JAMs), occludins, or claudins. The permeabilizing agent is typically a peptide or peptide analog or mimetic, often selected or derived from an extracellular domain of a mammalian JAM, occludin or claudin protein. Identification of candidate peptides derived from junctional adhesion mol. JAM-1, claudins and occludins is demonstrated. The effects of the peptides were tested in a com. airway epithelium model. Tests in adult male volunteers showed a significant improvement in the delivery of human interferon .beta. across the nasal mucosa when a peptide derived from JAM-1 was included in an intranasal formulation.

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L1 ANSWER 3 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:1002060 CAPLUS

TITLE: Impact of the selective **estrogen** receptor modulator, raloxifene, on neuronal survival and outgrowth following toxic insults associated with aging and Alzheimer's disease

AUTHOR(S): O'Neill, Kathleen; Chen, Shuhua; Brinton, Roberta Diaz

CORPORATE SOURCE: Pharmaceutical Sciences Center, Department of Molecular Pharmacology and Toxicology, University of Southern California, Los Angeles, CA, 90033, USA

SOURCE: Experimental Neurology (2004), 185(1), 63-80
CODEN: EXNEAC; ISSN: 0014-4886

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The current study investigated the **estrogen** agonist-antagonist properties of the selective **estrogen** receptor modulator, raloxifene (Ral), on neuroprotection and neuronal markers of memory function. Low concns. of raloxifene significantly reduced basal markers of membrane damage and had no deleterious effect on neuronal survival. However, high concns. of raloxifene (1000-5000 ng/mL) induced a significant increase in markers of membrane damage and a significant decrease in neuronal survival. At subtoxic concns., raloxifene induced significant neuroprotection against beta amyloid25-35-, hydrogen peroxide- and glutamate-induced toxicity. Results of analyses to det. whether raloxifene acted competitively or synergistically with 17 .beta.-estradiol revealed that a postmenopausal level of 17 .beta.-estradiol exerted a significantly greater increase in neuronal survival against beta-**amyloid**- and glutamate-induced toxicity compared to 50 ng/mL raloxifene. The combined presence of raloxifene and 17 .beta.-estradiol was significantly neuroprotective against beta amyloid25-35- and glutamate-induced excitotoxicity but was significantly lower than 17 .beta.-estradiol alone while not significantly different than raloxifene

alone. Morphol. analyses demonstrated that raloxifene significantly increased neuronal outgrowth of hippocampal neurons within a narrow dose range that was blocked by a glutamate NMDA receptor antagonist. Raloxifene did not promote the outgrowth of basal forebrain or cortical neurons. Results of this study indicate that raloxifene exerted partial **estrogen** agonist action in the absence of 17 .beta.-estradiol whereas in the presence of 17 .beta.-estradiol, raloxifene exerted a mixed **estrogen** agonist-antagonist effect.

L1 ANSWER 4 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:981428 CAPLUS
TITLE: The neuroprotective effects of **estrogen** in SK-N-SH neuroblastoma cell cultures
AUTHOR(S): Ba, Fang; Pang, Peter K. T.; Davidge, Sandra T.; Benishin, Christina G.
CORPORATE SOURCE: Faculty of Medicine, Department of Physiology, University of Alberta, Alta., Edmonton, T6G 2H7, Can.
SOURCE: Neurochemistry International (2004), 44(6), 401-411
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Estrogen** has been considered to be a neuroprotectant and a neuromodulator in many neuronal cell lines and tissue prepns. The protective effects of **estrogen** may be mediated through classical **estrogen** receptors (ERs), or may be due to its anti-oxidant properties which are independent of receptors. The current studies show that 17.beta.-estradiol (E2) is neuroprotective against .beta.-**amyloid** protein 25-35 (A.beta.)-, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-, high d. culture condition-, and serum deprivation-induced neuronal death in SK-N-SH human neuroblastoma cells. SK-N-SH cells express ER.beta., but not ER.alpha., as detected by Western blot anal. Among all the insults, MPTP, high d. culture and serum deprivation induce apoptotic cell death in this cell system as detected by ELISA detn. of mono/oligonucleosomes and DNA laddering, while A.beta. induces necrotic cell death. The protective effects of E2 are abolished by the addn. of tamoxifen and ICI 182,780 in the MPTP treated cells, but not in the other models, suggesting that the effect of E2 in the MPTP model is probably assocd. with activation of ER.beta.. The addn. of ICI 182,780 shows a mitogenic effect in SK-N-SH cells in the presence of E2 in control culture or in the A.beta. treated groups. Also, ICI 182,780 induced expression of ER.alpha.. Collectively, the current studies suggest that E2 is neuroprotective in apoptotic and necrotic death induced by multiple insults in SK-N-SH human neuroblastoma cells. Involvement of ER is insult type dependent. ICI 182,780 is able to influence the expression of ERs, probably through upregulation of ER.alpha. when ER.beta. is totally antagonized.

L1 ANSWER 5 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:973165 CAPLUS
TITLE: A comparison of the anti-inflammatory activities of conjugated **estrogens** and 17-.beta. estradiol
AUTHOR(S): Thomas, T. N.; Rhodin, J. A.; Clark, L.; Garces, A.; Bryant, M.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, 33612-4799, USA
SOURCE: Inflammation Research (2003), 52(11), 452-460
CODEN: INREFB; ISSN: 1023-3830
PUBLISHER: Birkhaeuser Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Unregulated chronic inflammatory process partly due to an **estrogen**

deficiency may render postmenopausal women vulnerable to degenerative conditions such as arthritis, osteoporosis, atherosclerosis, and Alzheimer's disease. Current confusion regarding therapeutic efficacy of **estrogen** replacement therapy may be due to different **estrogen** formulations used, short term therapy, as well as advanced stage of the disease. We compared anti-inflammatory activities of two major **estrogen** prepns., conjugated equine **estrogen** (CEE) and 17-.beta. estradiol, using an animal model (rat mesentery) of in vivo inflammatory reaction to i.v. infused **amyloid**-.beta., examd. by video recording and subsequently analyzed by transmission electron microscopy. Cellular markers of inflammation were monitored: leukocyte migration, platelet activation, mast cell activation/degranulation, and endothelial disruption. Low doses of CEE (0.3 mg/kg for 3 wk) demonstrated significant anti-inflammatory activity, whereas even at high doses (2.0 mg) 17-.beta. estradiol had only minimal activity. CEE, a mixt. of several compds., may have some component(s) with significant anti-inflammatory activity. The anti-inflammatory activity of CEE may have a role in prevention of several degenerative diseases assocd. with menopause.

L1 ANSWER 6 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:908210 CAPLUS
DOCUMENT NUMBER: 140:57735
TITLE: Hippocampal glucose metabolism is associated with cerebrospinal fluid **estrogen** levels in postmenopausal women with Alzheimer's disease
AUTHOR(S): Schoenknecht, Peter; Henze, Marcus; Hunt, Aoife; Klinga, Klaus; Haberkorn, Uwe; Schroeder, Johannes
CORPORATE SOURCE: Section of Geriatric Psychiatry, Department of Psychiatry, University of Heidelberg, Heidelberg, D-69115, Germany
SOURCE: Psychiatry Research (2003), 124(2), 125-127
CODEN: PSRSDR; ISSN: 0165-1781
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Animal studies indicate that **estrogens**, such as 17.beta.-estradiol (E2), may enhance hippocampal metab. and function. In postmenopausal Alzheimer's disease (AD) patients, cerebrospinal fluid (CSF) E2 levels were significantly lower than in non-demented controls. This finding was inversely correlated with CSF .beta.-**amyloid** levels. To address the potential impact of this finding, E2 levels in CSF were correlated with regional cerebral [18F]2-fluoro-2-deoxy-D-glucose (FDG) uptake as measured using positron emission tomog. (PET) in six postmenopausal AD patients. CSF E2 levels were detd. using an electro-chemiluminescence-immunoassay on the Roche Elecsys 2010 immunoassay analyzer. Basic image processing was done by MEDx, using SPM routines for spatial normalization and statistics. CSF E2 levels were significantly correlated with cerebral glucose metab. in the left hippocampus. This is the first clin. study indicating an assocn. between CSF E2 concn. and hippocampal glucose metab. in postmenopausal women with AD.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:864613 CAPLUS
TITLE: In vivo cerebrovascular actions of **amyloid** .beta.-peptides and the protective effect of conjugated **estrogens**
AUTHOR(S): Rhodin, Johannes A.; Thomas, Tom N.; Clark, Linda; Garces, Amanda; Bryant, Margaret

CORPORATE SOURCE: 12901 Bruce B. Downs Blvd, College of Medicine, Department of Anatomy, University of South Florida, MDC Box 6, Tampa, FL, 33612, USA
SOURCE: Journal of Alzheimer's Disease (2003), 5(4), 275-286
CODEN: JADIF9; ISSN: 1387-2877
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Vascular dysfunction and inflammatory processes may be early events in the pathol. of Alzheimer's disease (AD). Even though **amyloid** .beta.-peptides (A.beta.) play a prominent role in the initiation and progression of cellular dysfunction in AD, the precise in vivo actions of various A.beta.-peptides has not been established. The cerebrovascular actions of the major A.beta.-peptides (1-40) and (1-42) in live animals were investigated using an open cranial window technique. We show here that the A.beta.-peptides cause vascular lesions, esp. in the arterioles. In one set of expts., leukocytes and platelets were tagged with Rhodamine 6G, sol..beta.(1-40) infused i.v. for 2 min, and the vasculature video recorded for 90 min. In a second set of expts., sol..beta.(1-40) infusion was followed 30 min later by an infusion of sol. A.beta.(1-42) and the vasculature recorded for 90 min. Fluorescent and transmission electron microscopic examns. demonstrated the following cerebrovascular action of A.beta.-peptides: endothelial cell damage, leukocyte adhesion, platelet activation, thrombus formation, impeded blood flow, and smooth muscle cell damage. The vascular disruption obsd. were similar to those obsd. in the brains of some AD patients and may represent the initial phase of a vascular inflammatory response assocd. with cerebral **amyloid** angiopathy. The combination of A.beta.(1-40) and (1-42) produced significantly more vascular disruption than A.beta.(1-40) alone. Oral administration of conjugated **estrogens** in ovariectomized female rats protected them from the deleterious actions of A.beta.-peptides. The reported protective effect of **estrogen** against AD may be mediated in part through prevention of cerebrovascular A.beta. toxicity.

L1 ANSWER 8 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:828903 CAPLUS
TITLE: Estradiol prevents **amyloid**-.beta. peptide-induced cell death in a cholinergic cell line via modulation of a classical **estrogen** receptor
AUTHOR(S): Marin, R.; Guerra, B.; Hernandez-Jimenez, J.-G.; Kang, X.-L.; Fraser, J. D.; Lopez, F. J.; Alonso, R.
CORPORATE SOURCE: School of Medicine, Department of Physiology, Laboratory of Cellular Neurobiology, University of La Laguna, Santa Cruz de Tenerife, 38071, Spain
SOURCE: Neuroscience (Oxford, United Kingdom) (2003), 121(4), 917-926
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pathol. of Alzheimer's disease includes **amyloid**-.beta. peptide aggregation that contributes to degeneration of cholinergic neurons. Even though the underlying mol. mechanisms remain unclear, recent in vitro evidence supports a protective role for **estrogens** against several neurotoxic agents. Here we report that, in a murine cholinergic cell line (SN56), the massive cell death induced by 1-40 fragment of **amyloid**-.beta. peptide was prevented by 17.beta.-estradiol through a mechanism that may involve **estrogen** receptor activation. The protective effect of estradiol was obsd. in a dose-dependent manner, and was completely blocked by the pure antiestrogen ICI 182,780. In contrast, the inactive isomer 17.alpha.-estradiol

consistently showed weaker neuroprotection than the native hormone that was unaffected by ICI 182,780 treatment. In addn., equiv. concns. of 17.beta.-estradiol enhanced luciferase activity in cells transfected with a luciferase reporter gene driven by tandem **estrogen** response elements. **Estrogen**-induced luciferase activity was blocked by ICI 182,780, indicating **estrogen** receptor-dependent transcriptional activity. We also obsd. by reverse transcription-polymerase chain reaction, Western blot and immunocytochem. that increasing concns. of 17.beta.-estradiol enhanced the expression of **estrogen** receptor .alpha. mRNA and protein during **amyloid** -.beta.-induced toxicity. Under these conditions, it was found by confocal microscopy that the localization of **estrogen** receptor .alpha. in the absence of hormone was mainly extranuclear. However, the receptor was consistently obsd. also at the nuclear region after **estrogen** exposure. Overall, these data suggest that **estrogen** may exert neuroprotective effects against **amyloid** -.beta.-induced toxicity by activation of **estrogen** receptor-mediated pathways. In addn., intracellular **estrogen** receptors are up-regulated by their cognate hormone even during exposure to neurotoxic agents.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 9 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:825822 CAPLUS

TITLE: **Estrogen**-induced changes in the microtubular system correlate with a decreased susceptibility of aging neurons to beta **amyloid** neurotoxicity

AUTHOR(S): Shah, Ruchir D.; Anderson, Kelsi L.; Rapoport, Mark; Ferreira, Adriana

CORPORATE SOURCE: Department of Cell and Molecular Biology, Northwestern University, Chicago, IL, 60611, USA

SOURCE: Molecular and Cellular Neuroscience (2003), 24(2), 503-516
CODEN: MOCNED; ISSN: 1044-7431

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB A growing body of evidence suggests that **estrogen** has beneficial effects on Alzheimer's disease. However, the mechanisms underlying **estrogen**'s neuroprotective effects are not completely understood. In the present study, we analyzed first whether **estrogen** protects mature hippocampal neurons against fibrillar A.beta.-induced neurotoxicity. 17.alpha.-Estradiol and 17.beta.-estradiol partially prevented neuronal death induced by fibrillar A.beta.. **Estrogen** -induced neuroprotection correlated with the formation of a more dynamic microtubular system, including an increase in the pool of unstable microtubules and the expression of juvenile microtubule-assocd. proteins MAP2c and MAP1b. These results provide further evidence that exptl. conditions capable of increasing the pool of unstable microtubules might render mature hippocampal neurons resistant to the degeneration caused by fibrillar A.beta. deposits.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 10 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:814579 CAPLUS

TITLE: Inhibitory Effects of Bombusae concretio Salicea on Neuronal Secretion of Alzheimer's .beta.-**Amyloid** Peptides, a Neurodegenerative Peptide

AUTHOR(S): Jeong, Ji-Cheon; Kang, Sung-Koo; Yoon, Cheol-Ho; Seo, Young-Joon; Hwang, Cher-Won; Ko, Jeong-Heon; Lee,

Young-Choon; Chang, Young-Chae; Kim, Cheorl-Ho

CORPORATE SOURCE: College of Oriental Medicine, Department of Biochemistry and Internal Medicine, Dongguk University, Kyungju City, Kyungbuk 780-714, 780-714, S. Korea

SOURCE: Neurochemical Research (2003), 28(12), 1785-1792
CODEN: NEREDZ; ISSN: 0364-3190
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alzheimer's disease (AD) is characterized by the age-related deposition of .beta.-**amyloid** (A.beta.) 40/42 peptide aggregates in vulnerable brain regions. Multiple levels of evidence implicate a central role for A.beta. in the pathophysiol. of AD. A.beta. is generated by the regulated cleavage of a = 700 amino acid A.beta. precursor protein (.beta.APP). Full-length .beta.APP can undergo proteolytic cleavage either within the A.beta. domain to generate secreted s.beta.APP.alpha. or at the N-terminal and C-terminal domain(s) of A.beta. to generate amyloidogenic A.beta. peptides. Several epidemiol. studies have reported that **estrogen** replacement therapy protects against the development of AD in postmenopausal women. The aim of this study was to elucidate the antioxidant neuroprotective mechanism of Bombusae concretio Salicea (BC). BC was effective protectants against oxidative glutamate toxicity in the murine neuroblastoma cells (N2a) and human neuroblastoma cells (SK-N-MC). BC exhibited similar protective properties against oxidative glutamate toxicity and H2O2 toxicity. BC exhibited an antioxidant activity at approx. 20 .mu.g/mL. BC of 5 .mu.g/mL was ineffective in preventing the oxidative modification of LDL. The half-maximal effective concn. for BC was 16 .mu.g/mL. These results suggested that BC supplementation in elderly men may be protective in the treatment of Alzheimer's disease (AD). We report here that treatment with BC increases the secretion of the nonamyloidogenic APP fragment, s.beta.APP.alpha. and decreases the secretion of A.beta. peptides from N2a cells and rat primary cerebrocortical neurons. These results raise the possibility that BC supplementation in elderly men may be protective in the treatment of AD.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 11 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:795125 CAPLUS

TITLE: Protective effects of **estrogen** on **amyloid** beta-peptide 25-35-induced PC12 cell cytotoxicity

AUTHOR(S): Luo, Man; Xie, Rui-Man

CORPORATE SOURCE: Department of Gerontology, Zhongshan Hospital, Fudan University, Shanghai, 200032, Peop. Rep. China

SOURCE: Jiepouxue Zazhi (2003), 26(4), 360-363
CODEN: JZAZEF; ISSN: 1001-1633
PUBLISHER: Jiepouxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Expts. were carried out to study the effects of 17.beta.-estradiol on **amyloid** .beta.-peptide fragment 25-35 (A.beta.25-35)-induced PC12 cells cytotoxicity. PC12 cells were exposed to A.beta.25-35 of various concns. or treated with 17.beta.-estradiol before exposure to A.beta.25-35. The cell count, MTT metabolic rate and LDH leakage rate were used to measure the viability of PC12 cells. A dose-dependent decrease in cell count and MTT metabolic rate, and a dose-dependent increase in LDH leakage rate were found in the PC12 cells exposed to A.beta.25-35. An elevation of cell count and MTT metabolic rate, and a decrease in LDH leakage rate were revealed in the PC12 cells treated with 17.beta.-estradiol before exposure to A.beta.25-35. Thus,

17.beta.-estradiol may be useful to reduce A.beta.25-35-induced PC12 cells cytotoxicity.

L1 ANSWER 12 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:775820 CAPLUS
DOCUMENT NUMBER: 140:23373
TITLE: Potential use of **estrogen**-like drugs for the prevention of Alzheimer's disease
AUTHOR(S): Smith, Jonathan D.; Levin-Allerhand, Justine A.
CORPORATE SOURCE: Department of Cell Biology, NC10, The Cleveland Clinic Foundation, Cleveland, OH, 44195, USA
SOURCE: Journal of Molecular Neuroscience (2003), 20(3), 277-281
CODEN: JMNEES; ISSN: 0895-8696
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Prior epidemiol. studies have shown decreased incidence of Alzheimer's disease among women who were long-term users of hormone replacement therapy. In vitro studies have shown that **estrogens** possess antioxidant activity, protect cells from the cytotoxic effect of .beta.-**amyloid** peptides, and decrease the amyloidogenic processing of the **amyloid** precursor protein. Animal studies have shown that **estrogens** promote neuronal plasticity and lead to decreased levels of cerebral .beta.-**amyloid** peptide accumulation via decreased amyloidogenic processing of the **amyloid** precursor protein. Recently, a randomized double-blind placebo-controlled study of the effects of **estrogen** plus progestin treatment in women over 65 yr of age found that this treatment was assocd. with increased incidence of probable dementia. It is not known whether this combination of hormones or the late age at which the therapy was administered was responsible for the adverse outcome.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 13 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:755935 CAPLUS
DOCUMENT NUMBER: 139:301173
TITLE: Noncholinergic treatment options for Alzheimer's disease
AUTHOR(S): Sano, Mary
CORPORATE SOURCE: Bronx Veterans Medical Research Development, Bronx, NY, 10468-3904, USA
SOURCE: Journal of Clinical Psychiatry (2003), 64(Suppl. 9), 23-28
CODEN: JCLPDE; ISSN: 0160-6689
PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Approved treatments for Alzheimer's disease have focused primarily on cholinergic enhancement. New attention, however, is being turned toward preventative treatments such as vitamin E, **estrogen**, and lipid-lowering agents. Preventative treatments focus on intervening prior to the onset of disease. These treatments are designed to modify the **amyloid** load. These new approaches require designs that select nonimpaired or minimally impaired populations, using new outcomes with prolonged assessment. The cost of these studies is high, but the potential benefit of delay or prevention of disease is the valuable goal.
REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 14 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:705491 CAPLUS
DOCUMENT NUMBER: 139:362901
TITLE: Overexpression of superoxide dismutase 1 protects against .beta.-**amyloid** peptide toxicity: effect of **estrogen** and copper chelators
AUTHOR(S): Celsi, Fulvio; Ferri, Alberto; Casciati, Arianna; D'Ambrosi, Nadia; Rotilio, Giuseppe; Costa, Alfredo; Volonte, Cinzia; Carri, Maria Teresa
CORPORATE SOURCE: Fondazione Santa Lucia IRCCS, Rome, Italy
SOURCE: Neurochemistry International (2003), Volume Date 2004, 44(1), 25-33
CODEN: NEUIDS; ISSN: 0197-0186
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .beta.-**Amyloid** peptides (A.beta.) are major constituents of senile plaques in Alzheimer's disease (AD) brain and contribute to neurodegeneration, operating through activation of apoptotic pathways. It has been proposed that A.beta. induces death by oxidative stress, possibly through the generation of peroxy-nitrite from superoxide and nitric oxide. **Estrogen** is thought to play a protective role against neurodegeneration through a variety of mechanisms including scavenging of reactive oxygen species (ROS). In this study, we have challenged with A.beta., either in the presence or in the absence of 17.beta.-estradiol, differentiated human neuroblastoma SH-SY5Y cells (named line SH) and the same line overexpressing anti-oxidant enzyme superoxide dismutase 1 (SOD1; named line WT). We have obsd. that: (1) WT cells are less susceptible than SH cells to A.beta. insult; (2) caspase-3, but not caspase-1, is involved in A.beta.-induced apoptosis in this system; (3) **estrogen** protects both lines, without significantly affecting SOD activity; and (4) copper chelators prevent A.beta.-induced toxicity. Our results further support the notion that anti-oxidant therapy might be beneficial in the treatment of AD by preventing activation of selected apoptotic pathways.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 15 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:696523 CAPLUS
DOCUMENT NUMBER: 139:229271
TITLE: Signature genes expressed the lung during asthma or allergies and their use in predicting, diagnosing and treating asthma or allergies
INVENTOR(S): Rothenberg, Marc Elliot; Zimmermann, Nives
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 36 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003166562 | A1 | 20030904 | US 2003-377998 | 20030228 |
| WO 2003073990 | A2 | 20030912 | WO 2003-US6183 | 20030228 |

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-361606P P 20020301

AB Several genes are upregulated in the lung of asthma or allergy sufferers. Many of the genes up-regulated in asthma are involved in arginine metab. in the lung. Moreover, a set of 291 signature genes was found that can be used to indicate a patient's predilection for developing asthma or the patient's degree of suffering. Also, a set of 59 signature genes were found that indicate a patient's predilection for developing allergies. Many of the up-regulated genes relating to asthma were from the arginine metabolic pathway. Other genes, such as ADAM8, SPRR2A and SPRR2B were also strongly up-regulated in asthma. Treatment of asthma may be accomplished by administering compns. which decrease the levels of Arginase I, Arginase II, cationic amino acid transporter CAT2, or other arginase pathway members in the lung. Addnl., detection of altered levels of these proteins or the mRNA encoding them may be useful to diagnose the presence of asthma in a patient.

L1 ANSWER 16 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:670252 CAPLUS

TITLE: The glutamatergic system and Alzheimer's disease: therapeutic implications

AUTHOR(S): Butterfield, D. Allan; Pocernich, Chava B.

CORPORATE SOURCE: Department of Chemistry, Center of Membrane Sciences and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

SOURCE: CNS Drugs (2003), 17(9), 641-652
CODEN: CNDREF; ISSN: 1172-7047

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Alzheimer's disease affects nearly 5 million Americans currently and, as a result of the baby boomer cohort, is predicted to affect 14 million Americans and 22 million persons totally worldwide in just a few decades. Alzheimer's disease is present in nearly half of individuals aged 85 yr. The main symptom of Alzheimer's disease is a gradual loss of cognitive function. Glutamatergic neurotransmission, an important process in learning and memory, is severely disrupted in patients with Alzheimer's disease. Loss of glutamatergic function in Alzheimer's disease may be related to the increase in oxidative stress assocd. with the **amyloid** .beta.-peptide that is found in the brains of individuals who have the disease. Therefore, therapeutic strategies directed at the glutamatergic system may hold promise. Therapies addressing oxidative stress induced by hyperactivity of glutamate receptors include supplementation with **estrogen** and antioxidants such as tocopherol (vitamin E) and acetylcysteine (N-acetylcysteine). Therapy for hypoactivity of glutamate receptors is aimed at inducing the NMDA receptor with glycine and cycloserine (D-cycloserine). Recently, memantine, an NMDA receptor antagonist that addresses the hyperactivity of these receptors, has been approved in some countries for use in Alzheimer's disease.

REFERENCE COUNT: 137 THERE ARE 137 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 17 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:613112 CAPLUS

DOCUMENT NUMBER: 139:239448

TITLE: Perspectives on the pharmacological treatment of dementia

AUTHOR(S): Imbimbo, Bruno P.; Pomara, Nunzio
CORPORATE SOURCE: Research and Development, Chiesi Farmaceutici, Parma, Italy
SOURCE: Medical Psychiatry (2003), 20(Handbook of Medical Psychiatry), 865-897
CODEN: MEPSEN
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, discussing the major treatment strategies that are being pursued in dementia, esp. in Alzheimer's disease; these include anti-.beta.-**amyloid** therapies, anti-inflammatory drugs, antioxidants, **estrogens**, and statins.
REFERENCE COUNT: 279 THERE ARE 279 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 18 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:591420 CAPLUS
DOCUMENT NUMBER: 139:144404
TITLE: Methods for determining drug responsiveness
INVENTOR(S): Whitehead, Alexander S.; Challberg, Sharon S.; Lazar, James G.
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003062792 | A2 | 20030731 | WO 2003-US1651 | 20030122 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003138781 | A1 | 20030724 | US 2002-45360 | 20020122 |

PRIORITY APPLN. INFO.: US 2002-45360 A 20020122
US 2002-370008P P 20020403

AB The invention provides a diagnostics assay for measuring the responsiveness to a drug by comparing the mRNA levels of a gene that responds to the drug, such as a steroid, to the mRNA levels of a gene that does not respond to the drug. Methods according to the invention are useful for predicting the ability of a patient (or a tissue, body fluid or cell sample in vitro) to respond to a drug or steroid at any stage of their treatment (i.e., before, during or after), and to monitor the patient (or a tissue, body fluid or cell) over time to assess continued responsiveness to the drug or steroid.

L1 ANSWER 19 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:575349 CAPLUS
DOCUMENT NUMBER: 139:317654
TITLE: An **estrogen** replacement therapy containing

nine synthetic plant-based conjugated **estrogens** promotes neuronal survival

AUTHOR(S): Zhao, Lixia; Chen, Shuhua; Brinton, Roberta D.

CORPORATE SOURCE: Department of Molecular Pharmacology & Toxicology and Neuroscience Program, Pharmaceutical Sciences Center, University of Southern California, Los Angeles, CA, 90089, USA

SOURCE: Experimental Biology and Medicine (Maywood, NJ, United States) (2003), 228(7), 823-835
CODEN: EBMMBE; ISSN: 1535-3702

PUBLISHER: Society for Experimental Biology and Medicine

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Epidemiol. data from retrospective and case-control studies have indicated that **estrogen** replacement therapy can decrease the risk of developing Alzheimer's disease. In addn., **estrogen** replacement therapy has been found to promote neuronal survival both in vivo and in vitro. We have shown that conjugated equine **estrogens** (CEE), contg. 238 different mols. composed of **estrogens**, progestins, and androgens, exerted neurotrophic and neuroprotective effects in cultured neurons. In the current study, we sought to det. whether a steroidal formulation of nine synthetic conjugated **estrogens** (SCE) chem. derived from soybean and yam exts. is as effective as the complex multi-steroidal formulation of CEE. Analyses of the neuroprotective efficacy indicate that SCE exhibited significant neuroprotection against beta **amyloid**, hydrogen peroxide, and glutamate-induced toxicity in cultured hippocampal neurons. Indexes of neuroprotection included an increase in neuronal survival, a decrease in neurotoxin-induced lactate dehydrogenase release, and a redn. in neurotoxin-induced apoptotic cell death. Furthermore, SCE was found to attenuate excitotoxic glutamate-induced [Ca2+]i rise. Quant. analyses indicate that the neuroprotective efficacy of SCE was comparable to that of the multi-steroidal CEE formulation. Data derived from these investigations predict that SCE could exert neuroprotective effects comparable to CEE in vivo and therefore could reduce the risk of Alzheimer's disease in post-menopausal women.

REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 20 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:570526 CAPLUS

DOCUMENT NUMBER: 139:79535

TITLE: Methods for determining responsiveness to a steroid or drug by measuring mRNA levels of genes anticipated to respond to the drug

INVENTOR(S): Whitehead, Alexander Steven

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 28 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003138781 | A1 | 20030724 | US 2002-45360 | 20020122 |
| WO 2003062792 | A2 | 20030731 | WO 2003-US1651 | 20030122 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD,
RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-45360 A 20020122
US 2002-370008P P 20020403

AB The invention provides a diagnostics assay for measuring the responsiveness to a drug by comparing the mRNA levels of a gene that responds to the drug, such as a steroid, to the mRNA levels of a gene that does not respond to the drug. Methods according to the invention are useful for predicting the ability of a patient (or a tissue, body fluid or cell sample in vitro) to respond to a drug or steroid at any stage of their treatment (i.e., before, during or after), and to monitor the patient (or a tissue, body fluid or cell) over time to assess continued responsiveness to the drug or steroid. A kit for detg. steroid responsiveness is also claimed.

L1 ANSWER 21 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:532691 CAPLUS
DOCUMENT NUMBER: 139:95435
TITLE: Modified receptors on cell membranes for the discovery of therapeutic ligands
INVENTOR(S): Schwartz, Thue W.; Martini, Lene; Heydorn, Arne; Jorgensen, Rasmus
PATENT ASSIGNEE(S): 7TM Pharma A/S, Den.
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003055914 | A2 | 20030710 | WO 2002-DK900 | 20021220 |
| WO 2003055914 | A3 | 20031023 | | |

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 2001-1944 A 20011221
DK 2002-113 A 20020122
DK 2002-1043 A 20020703
US 2002-394122P P 20020703

AB A drug discovery method is provided for selecting a compd. selected from the group consisting of a small org. substance, a biopharmaceutical, or an antibody or part thereof. The method comprises the steps of (i) expressing one or more receptors on a cell membrane, such as, e.g., an exterior cell surface of a cell, (ii) contacting one or more expressed receptors with a test compd. or a selection of test compds. (libraries), and (iii) selecting one or more compds. based on its ability to bind one or more receptors. The step of expressing the one or more receptors

comprises capturing one or more receptors on the exterior cell surface in a conformation that predominantly enables binding or interaction with a ligand, and the conformation that predominantly enables binding or interaction with a ligand is provided by modification of one or more receptors by a method comprising at least one of the following: (a) fusion with any protein which keeps the receptor in the desired conformation such as, e.g. an arrestin, a modified arrestin, a G-protein or a modified G-protein, (b) site-directed mutagenesis, and (c) deletion. The receptors may be captured on the exterior cell surface by at least one of the following: (d) interaction of the receptor with a scaffolding protein, optionally, with a scaffolding protein network and (e) means for blocking receptor internalization, e.g. by co-expression of a mutated dynamin or a modified arrestin or by use of chems. such as, e.g., sucrose and/or Tris. Thus, by coexpressing of either the wild-type receptor or by modifying the receptor by engineering for example a recognition motif for a strong binder into its structure (for example, a PDZ recognition motif at its C-terminal end), and coexpression of this with a scaffolding protein such as PSD-95 or a modified scaffolding protein which interacts with the cytoskeleton at the cell surface or is made to be closely assocd. with the membrane through a lipid anchor, a high level of surface expression can be ensured, which will benefit its use in the drug discovery process. As a result of the strong tendency of the scaffolding proteins to interact with each other, just the cotransfection with one or more appropriate scaffolding proteins or modified scaffolding protein may also lead to the formation of patches with high local concns of the receptor or modified receptor, which will be highly beneficial in the drug discovery process where they are used initially to select binding mols. The method is exemplified by expression of the NK1 receptor in an agonist high-affinity binding form at the surface of transfected cells through fusion with arrestin or the N-terminal fragment of arrestin.

L1 ANSWER 22 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:499766 CAPLUS
DOCUMENT NUMBER: 139:174013
TITLE: Differentiation-dependent expression of 17.beta.-hydroxysteroid dehydrogenase, type 10, in the rodent testis: Effect of aging in Leydig cells
AUTHOR(S): Ivell, Richard; Balvers, Marga; Anand, Ravinder J. K.; Paust, Hans-Joachim; McKinnell, Chris; Sharpe, Richard
CORPORATE SOURCE: Institute for Hormone and Fertility Research, University of Hamburg, Hamburg, 22529, Germany
SOURCE: Endocrinology (2003), 144(7), 3130-3137
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expression of the new 17.beta.-hydroxysteroid dehydrogenase (HSD), type 10 (17.beta.-HSD-10), formerly known as endoplasmic reticulum-assocd. **amyloid**-binding protein, has been investigated in the testes of various mammals under normal and perturbed conditions. Results show that 17.beta.-HSD-10 is a major product of both fetal and adult-type Leydig cells. In the former, protein persists until late in postnatal development; and in the short-day hamster model, it does not disappear when Leydig cells involute. During puberty in the rat, immunohistochem. staining for 17.beta.-HSD-10 in adult-type Leydig cells first becomes evident on d 20, increasing to maximal staining intensity by d 35. In the rat, but not in the mouse or any other species examd., there is also staining in late spermatids. Examn. of testes from rats subjected to perinatal treatment with either a GnRH antagonist or low and high doses of diethylstilbestrol revealed that expression of 17.beta.-HSD-10 follows closely Leydig cell differentiation status, correlating with 3.beta.-HSD expression in a previous study. In aging (23 mo) rat testes, Leydig cell

(but not germ cell) immunostaining for 17.beta.-HSD-10 is markedly reduced. 17.beta.-HSD-10 seems to preferentially convert 3.alpha.-androstanediol into dihydrotestosterone, and estradiol to estrone. Thus, perinatal expression of this enzyme in fetal Leydig cells may contribute to protecting these cells from **estrogens** and encourage androgen formation.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 23 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:492204 CAPLUS
DOCUMENT NUMBER: 139:64331
TITLE: Modular biochip arrays and their diagnostic or analytical uses and their preparation and uses
INVENTOR(S): Bignon, Yves Jean; Vidal, Veronique; D'Incan, Chantal; Laplace, Chambaud Valerie; Sylvain, Vidal Valerie
PATENT ASSIGNEE(S): Centre Medico Chirurgical De Tronquieres, Fr.
SOURCE: Fr. Demande, 124 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| FR 2833968 | A1 | 20030627 | FR 2001-16962 | 20011220 |

PRIORITY APPLN. INFO.: FR 2001-16962 20011220
AB A method of constructing microarrays for specific diagnostic or research purposes is described. The microarrays are made up of modular sections with each module contg. probes for a defined set of genes that can be assembled to give an array suitable for a specific purposes. The individual modules may be on sep. supports.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 24 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:446978 CAPLUS
DOCUMENT NUMBER: 139:207955
TITLE: An **estrogen** membrane receptor participates in estradiol actions for the prevention of **amyloid**-.beta. peptide1-40-induced toxicity in septal-derived cholinergic SN56 cells
AUTHOR(S): Marin, Raquel; Guerra, Borja; Morales, Araceli; Diaz, Mario; Alonso, Rafael
CORPORATE SOURCE: Laboratory of Cellular Neurobiology, Department of Physiology, School of Medicine, University of La Laguna, Sta. Cruz de Tenerife, 38071, Spain
SOURCE: Journal of Neurochemistry (2003), 85(5), 1180-1189
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although **estrogen** [17.beta.-estradiol (E2)]-related neuroprotection has been demonstrated in different models, the involvement of non-classical **estrogen** receptors (ERs) remains unexplored. Using the SN56 cholinergic cell line, the authors present evidence indicating that an ER assocd. with the plasma membrane participates in **estrogen**-dependent inhibition of cell death induced by **amyloid**-.beta. peptide (A.beta.) toxicity. Similarly to E2 alone, a 15-min exposure to estradiol-horseradish peroxidase (E-HRP) significantly reduced A.beta.-induced cell death. This effect was

decreased by the ER antagonist ICI 182,780 as well as by MC-20 antibody directed to a region neighboring the ligand-binding domain of ER.alpha.. Using confocal microscopy on unpermeabilized SN56 cells exposed to MC-20 antibody, the authors identified a protein at the plasma membrane level. Western blot anal. of purified SN56 cell membrane fractions using MC-20 antibody revealed the presence of one band with the same electrophoretic mobility as intracellular ER.alpha.. Using conjugated forms of the steroid, E-HRP and E2 conjugated to bovine serum albumin-FITC, the authors demonstrated by confocal microscopy that SN56 cells contain surface binding sites for E2. Binding of both conjugates was blocked by pre-incubation with E2 and decreased by either ICI 182,780 or MC-20 antibody in a concn.-dependent manner. Thus, a membrane-related ER that shares some structural homologies with ER.alpha. may participate in **estrogen**-mediated neuroprotection.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 25 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:415194 CAPLUS

DOCUMENT NUMBER: 139:317603

TITLE: Testosterone, but not non-aromatizable dihydrotestosterone, improves working memory and alters nerve growth factor levels in aged male rats

AUTHOR(S): Bimonte-Nelson, Heather A.; Singleton, Rachel S.; Nelson, Matthew E.; Eckman, Christopher B.; Barber, John; Scott, Tonetta Y.; Granholm, Ann-Charlotte E.

CORPORATE SOURCE: Department of Physiology and Neuroscience, Medical University of South Carolina, Charleston, SC, 29425, USA

SOURCE: Experimental Neurology (2003), 181(2), 301-312
CODEN: EXNEAC; ISSN: 0014-4886

PUBLISHER: Elsevier Science

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Recent studies have suggested that testosterone levels are lower in men with Alzheimer's disease and that testosterone treatment improves cognition in older men. Since testosterone can be aromatized to **estrogen**, testosterone's effects could be due to conversion into **estrogen**. We treated aged male rats with either testosterone or dihydrotestosterone (DHT), the latter of which is not aromatized to **estrogen**, in order to det. whether these treatments improve spatial working and ref. memory as assessed in the water radial arm maze. We also tested whether such effects are related to .beta.-**amyloid** levels in the hippocampus or neurotrophin levels in the hippocampus, entorhinal cortex, frontal cortex, or striatum. Aged rats made more errors than young rats on all memory measures. Testosterone, but not DHT, improved working memory and decreased hippocampal NGF protein in aged rats, while having no effect on .beta.-**amyloid**. However, higher .beta.-**amyloid** levels were correlated with poorer working memory performance in young rats. Neurotrophin levels in entorhinal cortex were pos. correlated with errors for all memory measures in androgen-treated rats. Similar to findings in human studies, in our study androgen treatment lowered circulating estradiol levels in aged rats, suggesting that androgen treatment exerts feedback to the hypothalamic pituitary axis and that conversion to **estrogen** may not be the underlying biol. mechanism of testosterone's effects on memory and growth factor levels. The ratio of estradiol to testosterone, or the actions of the aromatase enzyme itself, may be responsible for the obsd. effects. These data support the hypothesis that testosterone therapy in aging men may provide pos. effects on cognition and that neural regions that are linked to cognition, such as the hippocampus and/or entorhinal cortex, may be involved in such effects.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 26 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:397078 CAPLUS
DOCUMENT NUMBER: 138:397218
TITLE: Multi-parameter high throughput screening assays (MPHTS) for identifying therapeutic compounds for treatment of neuropsychiatric and neurodegenerative disorders
INVENTOR(S): Altar, Anthony C.; Brockman, Jeffrey A.; Evans, David; Hook, Derek; Klimczak, Leszek; Laeng, Pascal; Palfreyman, Michael; Rajan, Prithi
PATENT ASSIGNEE(S): Psychiatric Genomics, Inc., USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003042654 | A2 | 20030522 | WO 2002-US31106 | 20020927 |
| WO 2003042654 | C2 | 20030807 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003096264 | A1 | 20030522 | US 2002-175523 | 20020618 |

PRIORITY APPLN. INFO.:
US 2001-333047P P 20011114
US 2002-349936P P 20020118
US 2002-361834P P 20020304
US 2002-175523 A 20020618
US 2001-299151P P 20010618
US 2001-317828P P 20010907
US 2001-325150P P 20010925

AB The present invention relates to screening methods and assays that are referred to herein as multi-parameter hight throughput screening (MPHTS) assays. These methods pertain to the combination of data generated from gene expression profiling coupled with methods for the systematic anal. and/or employment of such data. Such methods comprise steps of: identifying a plurality of disease signature genes and identifying a plurality of drug signature genes, followed by obtaining a score value for each of these genes that is a function of each gene's differential expression in the disease signature compared to its expression in the drug signature. Once scored, disease signature and drug signature genes having the highest score(s) may then ben selected as efficacy genes. Large nos. of candidate compds may be screened in vitro to identify ones that are particularly suitable and promising as novel therapeutic agents. These MPHTS assays are useful for identifying candidate pharmaceutical compds. In particular, the screening methods of this invention may be used to identify compds. that have potential therapeutic benefits for the treatment of neuropsychiatric and neurodegenerative disorders, including schizophrenia, bipolar affective disorder (BAD), autism, and Alzheimer's

disease to name a few.

L1 ANSWER 27 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:343890 CAPLUS
DOCUMENT NUMBER: 139:224611
TITLE: Double blind, randomized study of estradiol replacement therapy on markers of inflammation, coagulation and fibrinolysis
AUTHOR(S): Zegura, Branka; Keber, Irena; Sebestjen, Miran; Koenig, Wolfgang
CORPORATE SOURCE: Clinical Department of Gynecology and Obstetrics, Maribor Teaching Hospital, Maribor, 2000, Slovenia
SOURCE: Atherosclerosis (Shannon, Ireland) (2003), 168(1), 123-129
CODEN: ATHSBL; ISSN: 0021-9150
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Estrogen** replacement therapy (ERT) has been found to be assocd. with increased cardiovascular risk in the first year after initiation of ERT. We compared the effects of oral and transdermal estradiol (E2) replacement therapy on markers of inflammation, coagulation and fibrinolysis in a randomized double-blind trial. Forty-three healthy women were randomized 6 wk after surgically induced menopause to receive treatment with either oral or transdermal E2 over a period of 28 wk. At baseline and after 28 wk, levels of serum lipids and lipoproteins, and markers of coagulation, fibrinolysis and inflammation were detd. Among fibrinolytic parameters, oral E2 shortened euglobulin clot lysis time ($P<0.05$) and reduced tissue type plasminogen activator antigen ($P=0.01$) and plasminogen activator inhibitor activity ($P<0.05$). Among coagulation parameters, both routes of E2 replacement decreased fibrinogen levels ($P=0.002$ for oral and $P=0.007$ for transdermal E2). Oral E2 resulted in an increase in C-reactive protein (CRP) from 2.15 (0.71-4.05) to 3.41 (1.12-5.92) mg/l ($P=0.04$), while transdermal E2 showed no effect. Levels of serum **amyloid** A (SAA), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-.alpha.) did not change significantly after oral and transdermal E2. Oral E2 significantly improved the lipid profile, while transdermal E2 had a less pronounced effect. Both oral and transdermal E2 significantly reduced fasting glucose. Oral E2 was assocd. with a pro-inflammatory response, but at the same time improved fibrinolytic capacity, showed no pro-coagulatory effects, and acted beneficially on lipids and lipoproteins. There was no influence of transdermal E2 on markers of coagulation activation, fibrinolysis and inflammation, but it decreased fibrinogen levels significantly. Further studies are needed to explore the clin. relevance of these observations.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 28 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:343663 CAPLUS
DOCUMENT NUMBER: 139:286484
TITLE: Scavenger receptor class B type I expression in murine brain and regulation by **estrogen** and dietary cholesterol
AUTHOR(S): Srivastava, Rai Ajit K.
CORPORATE SOURCE: CloneGen Biotechnology, Ann Arbor, MI, 48105, USA
SOURCE: Journal of the Neurological Sciences (2003), 210(1-2), 11-18
CODEN: JNSCAG; ISSN: 0022-510X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The scavenger receptor class B type I (SR-BI), a receptor for high-d. lipoproteins (HDL), facilitates cholesterol delivery to steroidogenic tissues, and brings excess body cholesterol to liver for excretion. Scavenger receptors are also involved in the internalization of aggregates of Alzheimer's disease (AD) **amyloid** .beta.-protein, and selective uptake of HDL-assocd. vitamin E in the brain. Therefore, modulation of the brain SR-BI may affect these processes. The present study examd. the expression of SR-BI receptors in murine brain and their regulation by estradiol administration and cholesterol feeding. Liver and brain appeared to express similar SR-BI transcripts. Expression of SR-BI was highest in the adrenals and lowest in the brain. In rats, estradiol administration decreased SR-BI in liver, but increased it in adrenals. In mice, **estrogen** treatment decreased hepatic SR-BI, but interestingly increased the levels of brain SR-BI mRNA. Cholesterol feeding did not alter mouse hepatic SR-BI mRNA, but increased brain SR-BI levels. ATP-binding cassette transporter A1 (ABCA1), involved in cellular cholesterol transport, increased in cholesterol-fed mouse liver, but did not show changes in the brain. These studies suggest that SR-B1 is expressed in the brain and regulated by hormonal and nutritional stimuli, which may influence the pathophysiol. of neurol. disorders like AD.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 29 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:324031 CAPLUS

DOCUMENT NUMBER: 139:316523

TITLE: Neuroprotective effect of genistein against beta **amyloid**-lnduced neurotoxicity

AUTHOR(S): Bang, Oh Young; Mook, In Hee; Huh, Kyoon

CORPORATE SOURCE: Department of Neurology and Brain Disease Research Center, Ajou University, School of Medicine, Paldal-gu, Suwon-si, 442-749, S. Korea

SOURCE: Taehan Sin'gyong Kwahak Hoechi (2003), 21(2), 174-182 CODEN: TSKHC2; ISSN: 1225-7044

PUBLISHER: Korean Neurological Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: **Estrogen** is beneficial to patients with Alzheimer's disease but has a limited clin. use due to its proliferative and oncogenic effects on non-neuronal **estrogen** responsive cells. Methods: In an attempt to find an **estrogen** substitute that retains the beneficial effects of **estrogen** with minimal side effects, we compared the neuroprotective and proliferative effects of genistein, a selective **estrogen** receptor .beta. agonist, with those of **estrogen**. Results: Genistein and 17.beta.-estradiol showed comparable levels of protection against A.beta.-induced death of cultured SH-SY5Y human neuroblastoma cells, which was blocked by an **estrogen** receptor antagonist, ICI 182,780. On the other hand, 17.beta.-estradiol, but not geninstein, induced proliferation of uterine endometrial cells. Conclusions: Our results suggest genistein as a potential alternative to **estrogen** in the treatment of Alzheimer's disease.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 30 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:311316 CAPLUS

DOCUMENT NUMBER: 139:131425

TITLE: **Estrogen**-induced cell signaling in a cellular model of Alzheimer's disease

AUTHOR(S): Goodenough, S.; Schafer, M.; Behl, C.

CORPORATE SOURCE: Institute of Physiological Chemistry and

Pathobiochemistry, Johannes Gutenberg University, Mainz, 55099, Germany
SOURCE: Journal of Steroid Biochemistry and Molecular Biology (2003), 84(2-3), 301-305
CODEN: JSBBEZ; ISSN: 0960-0760
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Alzheimer's disease (AD) is characterized by deposition of a 4 kDa **amyloid**-.beta. peptide (A.beta.) into senile plaques of the affected brain. A.beta. is a proteolytic product of the membrane protein, **amyloid** precursor protein (APP). An alternative cleavage pathway involves .alpha.-secretase activity and results in secretion of a 100 kDa non-amyloidogenic APP (sAPP.alpha.) and therefore a potential redn. in A.beta. secretion. We have shown that **estrogen** induces .alpha.-cleavage and therefore results in the secretion of sAPP.alpha.. This secretion is signaled via MAP-kinase and PI-3 kinase signal-transduction pathways. These pathways also have the potential to inhibit the activation of glycogen synthase kinase 3.beta. (GSK), a protein involved in cell death. Therefore, the aim of this work was to further elucidate the **estrogen**-mediated signaling pathways involved in APP processing, with particular emphasis on GSK activity. By stimulating rat hypothalamic neuronal GT1-7 cells with estradiol, we found that **estrogen** decreases the activation state of GSK via the MAP kinase pathway. Moreover, the inhibition of GSK activity by LiCl causes enhanced sAPP.alpha. secretion in a pattern similar to that seen in response to **estrogen**, suggesting a pivotal role for this deactivation in APP processing. Further, inactivation of GSK by **estrogen** can be confirmed in an in vivo model. Elucidation of the signaling pathways involved in APP processing may help to understand the pathol. of AD and may also prove beneficial in developing therapeutic strategies to combat AD.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 31 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:302114 CAPLUS
DOCUMENT NUMBER: 139:79094
TITLE: Protein expression changes in the sprague dawley rat liver proteome following administration of peroxisome proliferator activated receptor .alpha. and .gamma. ligands
AUTHOR(S): White, Ian R.; Man, Wai J.; Bryant, Duncan; Bugelski, Peter; Camilleri, Patrick; Cutler, Paul; Hayes, William; Holbrook, Joanna D.; Kramer, Kerstin; Lord, Peter G.; Wood, John
CORPORATE SOURCE: Departments of Genomic and Proteomic Sciences, Medicines Research Centre, GlaxoSmithKline Pharmaceuticals, Stevenage, SG1 2NY, UK
SOURCE: Proteomics (2003), 3(4), 505-512
CODEN: PROTC7; ISSN: 1615-9853
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor superfamily and are intimately involved in lipid metab. and energy homeostasis. Activation of these receptors in rodents can lead to hepatomegaly and ultimately hepatic carcinogenesis although the mechanisms by which these processes occur are poorly understood. To further our understanding of these processes and to discriminate between different PPAR mediated signaling pathways, a proteomic approach has been undertaken to identify changes in protein expression patterns in Sprague

Dawley rat liver following dosing with a PPAR.alpha. agonist (Wyeth 14643), a PPAR.gamma. agonist (Troglitazone) and a compd. with mixed PPAR.alpha./.gamma. agonist activity (SB-219994). Using one-and-two-dimensional electrophoresis of tissue lysates a diverse range of protein abundance changes was obsd. in these tissues. While a no. of these proteins have PPAR response elements (PPREs) in their resp. promoters, another group was detected whose expression has been documented to be sensitive to peroxisome proliferator administration. Most notably within these groups, proteins involved in lipid catabolism displayed increased expression following drug administration. A further subset of proteins, with less obvious biol. implications, also showed altered expression patterns. Where available, sequences upstream of the coding regions of genes not previously known to have PPREs were searched with positional consensus matrixes for the presence of PPREs in an attempt to validate these changes. Using such an approach putative PPAR.gamma. and PPAR.delta. response elements were discovered upstream of the tubulin .beta. coding region. There was limited overlap in obsd. protein abundance changes between the three groups, and where this was the case (cytosolic epoxide hydrolase, peroxisomal bifunctional enzyme, hydroxymethyl glutaryl CoA, synthase, long chain acyl-CoA thioesterase), expression of these proteins had previously been shown to be under the control of PPAR activity.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 32 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:290576 CAPLUS
DOCUMENT NUMBER: 139:34055
TITLE: Progress in molecular genetics of Alzheimer's disease
AUTHOR(S): Wakutani, Yosuke; Kowa, Hisanori; Isoe-Wada, Kenji; Urakami, Katsuya; Nakashima, Kenji
CORPORATE SOURCE: Department of Neurology, Institute of Neurological Sciences, Faculty of Medicine, Tottori University, Japan
SOURCE: Idenshi Igaku (2003), 7(1), 44-50
CODEN: IDIGF4; ISSN: 1343-0971
PUBLISHER: Medikaru Du
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review on mutations of the .beta. **amyloid** precursor protein and presenilin genes in Alzheimer's disease. The topics discussed are (1) causative genes of familial Alzheimer's disease including the .beta. **amyloid** precursor protein gene, presenilin genes, and other susceptible loci; (2) risk factors of sporadic Alzheimer's disease including genetic polymorphisms of the **estrogen** receptor-.alpha. gene, apolipoprotein E gene promoter and methylene tetrahydrofolate reductase (MTHFR) gene; and (3) genetic studies of Alzheimer's disease.

L1 ANSWER 33 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:262063 CAPLUS
DOCUMENT NUMBER: 138:283689
TITLE: Identification of modulatory molecules with transgenic cells expressing target protein genes from inducible promoters
INVENTOR(S): Brown, Steven J.; Dunnington, Damien J.; Clark, Imran
PATENT ASSIGNEE(S): Axiom Biotechnologies, Inc., USA
SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003027634 | A2 | 20030403 | WO 2002-US30249 | 20020923 |
| WO 2003027634 | A3 | 20031120 | | |

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| US 2003082511 | A1 | 20030501 | US 2001-965201 | 20010925 |

PRIORITY APPLN. INFO.: US 2001-965201 A 20010925

AB Methods for identifying an ion channel modulator, a target membrane receptor modulator mol., and other modulatory mols. are disclosed, as well as cells and vectors for use in those methods. A polynucleotide encoding target is provided in a cell under control of an inducible promoter, and candidate modulatory mols. are contacted with the cell after induction of the promoter to ascertain whether a change in a measurable physiol. parameter occurs as a result of the candidate modulatory mol. Thus, CHO cells were transformed with a vector contg. the mouse voltage-gated potassium channel KCNC1 gene controlled by a tetracycline-inducible promoter. A membrane potential assay was used to demonstrate inhibition of KCNC1 by 4-aminopyridine and BaCl2 in doxycycline-induced cells. A similar system is described for screening for modulators of ciliary neurotrophic factor receptors. In this case the assay comprises measurement of STAT3 protein phosphorylation.

L1 ANSWER 34 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:250730 CAPLUS
DOCUMENT NUMBER: 139:316236
TITLE: Pharmacotherapy for Alzheimer's Disease: 2002
AUTHOR(S): Knopman, David
CORPORATE SOURCE: Dep. of Neurol., Mayo Clinic, Rochester, MN, 55905, USA
SOURCE: Clinical Neuropharmacology (2003), 26(2), 93-101
CODEN: CLNEDB; ISSN: 0362-5664
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The intensity of interest in therapy for Alzheimer's disease (AD) has accelerated with each passing year. The nature of the effects of cholinesterase inhibitors has been refined with the publication of several studies that have examd. long-term therapy as well as different aspects of the symptomatol. of AD. Breakthroughs in the basic science of AD has led to new insights into potential therapeutic strategies targeted at the secretases involved in the metab. of the Alzheimer precursor protein. An immunization approach in which the **amyloid**-.beta. protein itself was used as the immunizing agent was discontinued after unexpected toxicity occurred. Other areas of investigation with disappointing results such as **estrogen** replacement therapy and antiinflammatory approaches are discussed. Several other potential therapeutic agents are also reviewed.

REFERENCE COUNT: 83 THERE ARE 83 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 35 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:242999 CAPLUS
DOCUMENT NUMBER: 139:1166
TITLE: **Estrogen** activates protein kinase C in neurons: Role in neuroprotection
AUTHOR(S): Cordey, Myriam; Gundimeda, Usha; Gopalakrishna, Rayudu; Pike, Christian J.
CORPORATE SOURCE: Neuroscience Graduate Program, Department of Cell and Neurobiology, University of Southern California, Los Angeles, CA, 90089-0191, USA
SOURCE: Journal of Neurochemistry (2003), 84(6), 1340-1348
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB It has been previously demonstrated that **estrogen** can protect neurons from a variety of insults, including .beta.-**amyloid** (A.beta.). Recent studies have shown that **estrogen** can rapidly modulate intracellular signaling pathways involved in cell survival. In particular, **estrogen** activates protein kinase C (PKC) in a variety of cell types. This enzyme plays a key role in many cellular events, including regulation of apoptosis. In this study, the authors show that 17.beta.-estradiol (E2) rapidly increases PKC activity in primary cultures of rat cerebrocortical neurons. A 1 h pretreatment with E2 or phorbol-12-myristate-13-acetate (PMA), a potent activator of PKC, protects neurons against A.beta. toxicity. Protection afforded by both PMA and E2 is blocked by pharmacol. inhibitors of PKC. Further, depletion of PKC levels resulting from prolonged PMA exposure prevents subsequent E2 or PMA protection. The authors' results indicate that E2 activates PKC in neurons, and that PKC activation is an important step in **estrogen** protection against A.beta.. These data provide new understanding into the mechanism(s) underlying **estrogen** neuroprotection, an action with therapeutic relevance to Alzheimer's disease and other age-related neurodegenerative disorders.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 36 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:238134 CAPLUS
DOCUMENT NUMBER: 138:234488
TITLE: Method for the determination of multiple disease markers in tissues
PATENT ASSIGNEE(S): Werner, M., Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| DE 10143757 | A1 | 20030327 | DE 2001-10143757 | 20010906 |

PRIORITY APPLN. INFO.: DE 2001-10143757 20010906

AB The invention concerns a method for the detn. of at least two disease markers in a tissue by using labeled antibodies, lectins or nucleic acids. Labels are fluorescent dyes or enzymes. Disease-causing microorganisms, antigens, epitopes. proteins, chromosomes, genes, oncogenes, tumor surpressants , nucleic acids are detd.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 37 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2003:176630 CAPLUS
DOCUMENT NUMBER: 138:352059
TITLE: Chlamydia trachomatis infection alters host cell transcription in diverse cellular pathways
AUTHOR(S): Xia, Minsheng; Bumgarner, Roger E.; Lampe, Mary F.; Stamm, Walter E.
CORPORATE SOURCE: Division of Infectious Diseases, Department of Medicine, University of Washington, Seattle, USA
SOURCE: Journal of Infectious Diseases (2003), 187(3), 424-434
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To study the responses of the host cell to chlamydial infection, differentially transcribed genes of the host cells were examd. Complementary DNA (cDNA) probes were made from mRNAs of HeLa cells infected with Chlamydia trachomatis and were hybridized to a high-d. human DNA microarray of 15,000 genes and expressed sequence tags. C. trachomatis alters host cell transcription at both the early and middle phases of its developmental cycle. At 2 h after infection, 13 host genes showed mean expression ratios .gtoreq.2-fold. At 16 h after infection, 130 genes were differentially transcribed. These genes encoded factors inhibiting apoptosis and factors regulating cell differentiation, components of the cytoskeleton, transcription factors, and proinflammatory cytokines. This indicates that chlamydial infection, despite its intravacuolar location, alters the transcription of a broad range of host genes in diverse cellular pathways and provides a framework for future studies.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 38 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:139094 CAPLUS
DOCUMENT NUMBER: 138:185476
TITLE: **Estrogen** and diet effects in vivo on cerebral apoE and beta-**amyloid**
AUTHOR(S): Levin-Allerhand, Justine Ariella
CORPORATE SOURCE: Rockefeller Univ., New York, NY, USA
SOURCE: (2002) 196 pp. Avail.: UMI, Order No. DA3053197
From: Diss. Abstr. Int., B 2002, 63(5), 2232
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L1 ANSWER 39 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:100534 CAPLUS
DOCUMENT NUMBER: 138:331900
TITLE: Application of cDNA microarray for uterotrophic assay
AUTHOR(S): Wong, Kwong-Kwok; Kanno, Jun; Cheng, Rita; Sasser, Lyle; Morris, James; Anderson, Larry; Pounds, Joel; Inoue, Tohru
CORPORATE SOURCE: Hematology/Oncology Section, Department of Pediatrics, Baylor College of Medicine, Texas Children's Cancer Center, Houston, TX, 77030, USA
SOURCE: Toxicogenomics (2003), 141-148. Editor(s): Inoue, Tohru; Pennie, William D. Springer-Verlag Tokyo: Tokyo, Japan.
CODEN: 69DOR9; ISBN: 4-431-70344-6
DOCUMENT TYPE: Conference
LANGUAGE: English
AB To develop a sensitive cDNA microarray based uterotrophic assay, ovariectomized mice were treated with a low dose of 17-.beta.-estradiol

(0.2 .mu.g/kg/day) over a three-day period. The av. increases in uterine wt. were 13%, 23% and 70% after treatment at day 1, day 2 and day 3 resp. Twenty-four hours after each treatment, uteri were dissected for total RNA extn. and gene expression profiles were assayed with a mouse cDNA microarray contg. more than 5000 cDNA elements. From the anal., we were able to detect 72 genes that were induced more than 2-fold 24 h after the ovariectomized mice were treated a single dose of 17-.beta.-estradiol. 49 Of these genes form a tight cluster when analyzed by the software OmniVizPro based on their temporal expression profiles. The no. of genes induced more than two-fold increases to more than 200 after the ovariectomized mice were treated with 17-.beta.-estradiol once a day for 1 or 2 more days. These inducible genes include both known and unknown genes. Identified known genes are involved in cell division, transcription activation, stress response, oncogene, and other biochem. activities. These results suggest that gene expression profiles can be used as an alternative endpoint for uterotrophic assay. Further anal. and exploitation of this set of genes will allow us to develop a more sensitive and specific assay for the detection of estrogenic chem. as well as the understanding of the signaling pathway elicited by 17-.beta.-estradiol.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 40 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:97550 CAPLUS
DOCUMENT NUMBER: 138:164674
TITLE: Molecular markers for hepatocellular carcinoma and their use in diagnosis and therapy
INVENTOR(S): Debuschewitz, Sabine; Jobst, Juergen; Kaiser, Stephan
PATENT ASSIGNEE(S): Germany
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003010336 | A2 | 20030206 | WO 2002-EP8305 | 20020725 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| DE 10136273 | A1 | 20030213 | DE 2001-10136273 | 20010725 |

PRIORITY APPLN. INFO.: DE 2001-10136273 A 20010725

AB The invention relates to mol. markers occurring for hepatocellular carcinoma. The invention more particularly comprises gene sequences or peptides coded thereby which can be regulated upwards or downwards for hepatic cell carcinoma (HCC) in relation to healthy, normal liver cells in the expression thereof. The invention also relates to the use of said sequences in the diagnosis and/or therapy of HCC and for screening purposes in order to identify novel active ingredients for HCC. The invention also relates to an HCC specific cluster as a unique diagnostic agent for HCC.

L1 ANSWER 41 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:58234 CAPLUS
DOCUMENT NUMBER: 138:105630
TITLE: Reduction of the stimulatory capacity of antigen-presenting cells
INVENTOR(S): Sheriff, Ahmed
PATENT ASSIGNEE(S): Genethor G.m.b.H., Germany
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003006636 | A1 | 20030123 | WO 2002-EP7740 | 20020711 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DE 2001-10133926 A 20010712
AB The invention relates to a method for reducing immune reactions. The inventive method is characterized by manipulating the stimulatory properties of antigen-presenting cells and optionally at the same time inducing the antigen-presenting cells to present defined antigens. The antigen-presenting cells are transfected with a nucleic acid coding for a defined antigen, and these cells present only this antigen. This antigen can be an autoantigen, allergen, or anything that causes an unwanted immune response. Also, the antigen-presenting cells contain nucleic acids which code for PD-1 binding mol. and/or CTLA-4 binding mol. and/or mols. which suppress the expression of CD83, eIF-5a, B7, and CD40. The antigen-presenting cells can be used in treatment of autoimmune disease, allergy, and transplantation.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 42 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:27749 CAPLUS
DOCUMENT NUMBER: 138:314795
TITLE: Protective effects of estradiol against **amyloid** .beta. protein-induced inhibition of neuronal Cl--ATPase activity
AUTHOR(S): Yagyu, K.; Kitagawa, K.; Wu, B.; Zhang, N.-Y.; Irie, T.; Hattori, N.; Inagaki, C.
CORPORATE SOURCE: Department of Pharmacology, Kansai Medical University, Moriguchi City, Osaka, 570-8506, Japan
SOURCE: Neuropharmacology (2003), Volume Date 2002, 43(8), 1297-1304
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Low concns. of **amyloid** .beta. proteins (A.beta.s, 1-10 nM) were

recently demonstrated to reduce Cl--ATPase activity in parallel with an increase in the intracellular Cl- concn. ([Cl-]i) and decreases in plasma membrane phosphorylated phosphatidylinositol (PIP and PIP2) levels in cultured rat hippocampal neurons. In this study, 17 .beta.-estradiol (estradiol) at a therapeutic concn. (1.8 nM) for Alzheimer's disease was found to block these A.beta. (A.beta.25-35)-induced changes. This protective effect of estradiol on Cl--ATPase activity was antagonized by a pure **estrogen** receptor antagonist, ICI182780 and inhibitors for cGMP-dependent protein kinase (PKG) (KT5823), Ca2+-calmodulin-dependent protein kinase II (CaMKII) (KN62) and phosphatidylinositol (PI) 4-kinase (wortmannin and quercetin). Estradiol recovered A.beta.-induced decreases in plasma membrane phosphoinositide (PIP and PIP2) levels, this effect being inhibited by KT5823 and KN62. Glutamate toxicity was augmented in neurons with elevated [Cl-]i either by A.beta.-treatment or carbachol+KCl+LiCl-treatment. The increased glutamate toxicity in the A.beta.-treated neurons was attenuated by estradiol. Thus, a therapeutic concn. of estradiol protected A.beta.-treated neurons against inhibition of Cl--ATPase activity and an increase in [Cl-]i through its receptor, probably via PKG- and CaMKII-mediated recovery of PI4P formation. Elevated [Cl-]i may be related to enhancement of glutamate toxicity.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 43 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:11325 CAPLUS
DOCUMENT NUMBER: 138:198882
TITLE: Pro-inflammatory effects of oestrogens during use of oral contraceptives and hormone replacement treatment
AUTHOR(S): Kluft, C.; Leuven, J. A. Gevers; Helmerhorst, F. M.; Krans, H. M. J.
CORPORATE SOURCE: Gaubius Laboratory, Vascular and Connective Tissue Research, TNO-PG, Leiden, 2333 CK, Neth.
SOURCE: Vascular Pharmacology (2002), 39(3), 149-154
CODEN: VPAHAJ; ISSN: 1537-1891
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of two third-generation monophasic combined oral contraceptives (COC) and a postmenopausal hormone replacement therapy (HRT) consisting of 2 mg 17.beta.-estradiol on the plasma level of the acute-phase indicator C-reactive protein (CRP) and other acute-phase reactants were analyzed. Two studies were conducted: (1) a randomized, open-label study with two different oral contraceptive prepns. with an equal dose of ethinylestradiol (EE) (30 .mu.g) and a different progestogen, either 75 .mu.g gestodene (GSD-EE) or 150 .mu.g desogestrel (DSG-EE); blood samples of 39 young women were analyzed before and after 3, 6, 12 treatment cycles; (2) a randomized, blinded placebo-controlled study with 2 mg 17.beta.-estradiol in postmenopausal women with non-insulin-dependent diabetes mellitus without signs of cardiac involvement; blood samples of 38 women were analyzed before and after 6 wk of treatment. The plasma concn. of CRP increased strongly during oral contraceptive use for both prepns.; the increase persisted over 12 cycles. The already elevated CRP in postmenopausal diabetic women showed a moderate increase after 6 wk of treatment with 17.beta.-estradiol. CRP increases during oral contraceptive use were assocd. with changes in some other acute-phase proteins (fibrinogen, ceruloplasmin, von Willebrand factor [vWF]) originating from the liver and vessel wall, but not in others (interleukin-6 [IL-6], serum **amyloid** A [SAA]). The results demonstrate an increase in a specific set of acute-phase reactants caused by **estrogen**-contg. prepns. It is proposed that the pro-inflammatory effect of **estrogens** should be checked for a relationship with the increased risk of thromboembolism for both oral

contraceptive and HRT.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 44 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:979723 CAPLUS
DOCUMENT NUMBER: 139:63531
TITLE: 17.alpha.-estradiol and 17.beta.-estradiol treatments are effective in lowering cerebral **amyloid** -.beta. levels in A.beta.PPSWE transgenic mice
AUTHOR(S): Levin-Allerhand, Justine A.; Lominska, Chris E.; Wang, Jennifer; Smith, Jonathan D.
CORPORATE SOURCE: The Rockefeller University, New York, NY, USA
SOURCE: Journal of Alzheimer's Disease (2002), 4(6), 449-457
CODEN: JADIF9; ISSN: 1387-2877
PUBLISHER: IOS Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Post-menopausal **estrogen** therapy is assocd. with a decreased incidence of Alzheimer disease and in vitro models have shown that 17.beta.-estradiol is effective in lowering amyloidogenic processing. To examine the effects of **estrogen** withdrawal and replacement on **amyloid** .beta. (A.beta.) levels and **amyloid** .beta.-protein precursor (A.beta.PP) processing in vivo, Swedish mutant A.beta.PP transgenic mice were ovariectomized or sham ovariectomized at four weeks of age and treated with placebo or 17.beta.- or 17.alpha.-estradiol pellets, the latter being a weak **estrogen** receptor agonist. Compared to sham ovariectomized mice, ovariectomy with placebo did not alter A.beta. levels; however, the levels of A.beta. were decreased by 27% with 17.beta.- and 17.alpha.- estradiol, resp., with no change in A.beta.PP holoprotein. Endogenous and exogenous **estrogen** both significantly increased the levels of sA.beta.PP.alpha., the secreted form of A.beta.PP. The ratio of A.beta./sA.beta.PP.alpha., a measure of amyloidogenic processing, was reduced in all **estrogen**-contg. groups. The A.beta. lowering effect of 17.beta.- and 17.alpha.-estradiol was replicated when **estrogens** were administered at a more physiol. dose in the drinking water, or when mice were ovariectomized at three months of age. The increased efficacy of 17.alpha.-estradiol vs. 17.beta.-estradiol may help to develop safe and effective therapeutics.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 45 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:968227 CAPLUS
DOCUMENT NUMBER: 138:285420
TITLE: Lipid metabolism, epidemiology, and the mechanisms of Alzheimer's disease
AUTHOR(S): Friedland, Robert P.
CORPORATE SOURCE: Laboratory of Neurogeriatrics, Department of Neurology, Case Western Reserve University School of Medicine, Cleveland, OH, 44106, USA
SOURCE: Annals of the New York Academy of Sciences (2002), 977(Alzheimer's Disease: Vascular Etiology and Pathology), 387-390
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Global variations in the incidence and prevalence of Alzheimer's disease (AD) have not been explained. Patterns of dietary intake of fats and other nutrients may be partly responsible. Recent work with transgenic

mice overexpressing the .beta.-**amyloid** precursor protein suggests that anti-A.beta. antibodies enhance clearance of the A.beta. protein from the brain and reduce plaque burden. This has been shown even with anti-A.beta. antibodies that do not enter the brain. Many factors other than circulating anti-A.beta. antibodies may influence this important process of AD clearance, including the A.beta.-binding elements, apolipoproteins E and J, circulating LDL, HDL, and LRP, alpha-2-macroglobulin, and transthyretin. Also important may be clearance of antibody-antigen complexes from the circulation, as well as complement, metals, and **estrogen**. Dietary intake of lipids may influence the ability of A.beta.-binding proteins to enhance clearance of A.beta. from the brain to blood. Understanding processes of A.beta. clearance from brain may aid in detg. the causes of AD in individuals, as well as the causes of global variations in incidence and prevalence of the disease.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 46 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:968223 CAPLUS

DOCUMENT NUMBER: 138:285419

TITLE: Cholesterol and cognition: Rationale for the AD cholesterol-lowering treatment trial and sex-related differences in .beta.-**amyloid** accumulation in the brains of spontaneously hypercholesterolemic Watanabe rabbits

AUTHOR(S): Sparks, D. Larry; Martins, Ralph; Martin, Tim

CORPORATE SOURCE: Roberts Laboratory for Neurodegenerative Disease Research, Sun Health Research Institute, Sun city, AZ, USA

SOURCE: Annals of the New York Academy of Sciences (2002), 977(Alzheimer's Disease: Vascular Etiology and Pathology), 356-366
CODEN: ANYAA9; ISSN: 0077-8923

PUBLISHER: New York Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This report presents the scientific rationale and hypothesis for the investigator-initiated, double-blind, placebo-controlled Alzheimer's Disease Cholesterol-Lowering Treatment Trial. As part of the supporting preclin. data, accumulation of neuronal .beta.-**amyloid** immunoreactivity was investigated in 12-mo-old male spontaneously hypercholesterolemic Watanabe rabbits, female Watanabe rabbits between 3 and >36 mo of age, and untreated female New Zealand white rabbits between 6 and 12 mo of age. Prior evidence suggests that there are significant accumulations of neuronal .beta.-**amyloid** immunoreactivity in the cholesterol-fed New Zealand white rabbit. At 3 mo of age, abundant .beta.-**amyloid** immunoreactive neurons are also found in female hypercholesterolemic Watanabe rabbits. By 6 mo of age, as female Watanabe rabbits are approaching sexual maturity, the no. of .beta.-**amyloid** immunoreactive neurons was somewhat reduced, but the intensity of the immunoreactivity was clearly and consistently diminished. Very few neurons expressing .beta.-**amyloid** immunoreactivity were identifiable among the 12-mo-old Watanabe female rabbits. Variably increased nos. of intensely stained .beta.-**amyloid** immunoreactive neurons were obsd. in retired breeder female animals over 3 yr of age. Twelve-month-old male Watanabe rabbits exhibited levels of neuronal .beta.-**amyloid** immunoreactivity consistent with younger and older female animals, but greater than the adult 12-mo-old females. Cholesterol levels in the blood were not noticeably different among females over the age range investigated or compared to 12-mo-old males. **Estrogen** levels varied with age in female Watanabe rabbits in an

apparent inverse relationship with neuronal .beta.-**amyloid** immunoreactivity. However, there was no evidence of increased neuronal .beta.-**amyloid** immunoreactivity in untreated female New Zealand white rabbits with "normal" circulating cholesterol levels at any age investigated. Therefore, under conditions of stable, but elevated, circulating cholesterol levels, pathol. accumulation of neuronal .beta.-**amyloid** immunoreactivity was similar in male Watanabe rabbits and female animals prior and subsequent to estrus. The intensity of observable neuronal .beta.-**amyloid** immunoreactivity accumulation decreases in female animals as circulating **estrogen** levels increased with sexual maturity. These data suggest that a loss of circulating **estrogen** could mark the collapse of a system previously protecting a female from conditions conducive to prodn. of .beta.-**amyloid** as a putative neurotoxin in AD. This may, in part, explain the epidemiol. evidence for "protective" effects of **estrogen** in AD.

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 47 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:968081 CAPLUS
DOCUMENT NUMBER: 138:32683
TITLE: Non-cholinergic strategies for treating and preventing Alzheimer's disease
AUTHOR(S): Doraiswamy, P. Murali
CORPORATE SOURCE: Departments of Psychiatry and Medicine, Duke University Medical Center, Durham, NC, USA
SOURCE: CNS Drugs (2002), 16(12), 811-824
CODEN: CNDREF; ISSN: 1172-7047
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The pathophysiol. of Alzheimer's disease is complex and involves several different biochem. pathways. These include defective .beta.-**amyloid** (A.beta.) protein metab., abnormalities of glutamatergic, adrenergic, serotonergic and dopaminergic neurotransmission, and the potential involvement of inflammatory, oxidative and hormonal pathways. Consequently, these pathways are all potential targets for Alzheimer's disease treatment and prevention strategies. Currently, the mainstay treatments for Alzheimer's disease are the cholinesterase inhibitors, which increase the availability of acetylcholine at cholinergic synapses. Since the cholinesterase inhibitors confer only modest benefits, addnl. non-cholinergic Alzheimer's disease therapies are urgently needed. Several non-cholinergic agents are currently under development for the treatment and/or prevention of Alzheimer's disease. These include anti-**amyloid** strategies (e.g. immunization, aggregation inhibitors, secretase inhibitors), transition metal chelators (e.g. clioquinol), growth factors, hormones (e.g. estradiol), herbs (e.g. Ginkgo biloba), nonsteroidal anti-inflammatory drugs (NSAIDs, e.g. indomethacin), antioxidants, lipid-lowering agents, antihypertensives, selective phosphodiesterase inhibitors, vitamins (E, B 12, B6, folic acid) and agents that target neurotransmitter or neuropeptide alterations. Neurotransmitter receptor-based approaches include agents that modulate certain, receptors (e.g. nicotinic, muscarinic, .alpha.-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid [AMPA], .gamma.-aminobutyric acid [GABA], N-methyl-D-aspartate [NMDA]) and agents that increase the availability of neurotransmitters (e.g. noradrenergic reuptake inhibitors). Of these strategies, the NMDA receptor antagonist memantine is in the most advanced stage of development in the US and is already approved in Europe as the first treatment for moderately severe to severe Alzheimer's disease. Memantine is proposed to counteract cellular damage due to pathol.

activation of NMDA receptors by glutamate. Results with Ginkgo biloba have been mixed. Data for neurotrophic therapies and vitamin E (tocopherol) appear promising but require confirmation. NSAIDs and conjugated **estrogens** have not proven to be of value to date for the treatment of Alzheimer's disease. Statins may have a potential role in reducing the risk or delaying the onset of Alzheimer's disease, although this has yet to be confirmed in randomized trials. There are currently no data to support the use of statins as a treatment for dementia. This article provides an update on the current status of selected agents, focusing primarily on those agents with the most extensive clin. evidence at present.

REFERENCE COUNT: 115 THERE ARE 115 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 48 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:937303 CAPLUS
DOCUMENT NUMBER: 138:20443
TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes
INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin
PATENT ASSIGNEE(S): Takara Bio Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| JP 2002355079 | A2 | 20021210 | JP 2002-69354 | 20020313 |

PRIORITY APPLN. INFO.:
JP 2001-73183 A 20010314
JP 2001-74993 A 20010315
JP 2001-102519 A 20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises prepg. a nucleic acid sample contg. mRNAs or cDNAs originating in cells, tissues, or organisms which have been brought into contact with a sample contg. the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-.beta. estradiol (E2), were found in mice by DNA chip anal.

L1 ANSWER 49 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:933950 CAPLUS
DOCUMENT NUMBER: 138:202924
TITLE: Animal model of **amyloid**-.beta. induced vascular inflammation and prevention by **estrogen** and other agents
AUTHOR(S): Rhodin, J.; Thomas, T.
CORPORATE SOURCE: Department of Anatomy, College of Medicine, University of South Florida, Tampa, FL, USA
SOURCE: World Congress for Microcirculation, submitted Papers, 7th, Sydney, Australia, Aug. 19-22, 2001 (2001),

543-547. Monduzzi Editore: Bologna, Italy.
CODEN: 69DILJ; ISBN: 88-323-1819-9
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Inflammatory processes play a prominent role in the pathol. of a no. of diseases ranging from arthritis, atherosclerosis, cancer and Alzheimer's disease. Utilizing a live animal (rat) model, and combining intravital video recordings of mesenteric microvascular bed with TEM analyses of the same vascular segments, the authors demonstrate inflammatory responses by arterioles and venules after infusion of **amyloid**-.beta.(1-40), the protein accumulating in brains of Alzheimer patients. The inflammatory responses were prevented by administering the following agents before the **amyloid**: (A) superoxide dismutase; (B) tumor necrosis factor-binding protein; (C) interleukin-1 receptor antagonist; (D) conjugated equine **estrogen**; (E) RAGE antibody.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 50 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:928122 CAPLUS
DOCUMENT NUMBER: 138:12504
TITLE: Method for assaying biomolecules and other constituents using indicator conjugates with synthetic nucleounits in lateral flow, liquid, and dry chemistry techniques
INVENTOR(S): Smith, Jack V.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 46 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002182600 | A1 | 20021205 | US 2001-829563 | 20010411 |

PRIORITY APPLN. INFO.: US 2001-829563 20010411
AB The present invention is a method for the use of particles made up of nucleotides or fragments of base groups of DNA and RNA mols. herein referred to as synthetic nucleounits which can be used as recognition mols. with specificity and sensitivity significantly greater than that of antibodies which are used in clin. diagnostics, biotechnol., and research. The method for detecting an analyte using nucleounits targeted to the analyte comprises (1) identifying a nucleounit from a mixt. of synthetic random sequences of nucleounit libraries, (2) conjugating the nucleounit to an indicator for the analyte, and (3) detecting the analyte using the nucleounit-indicator conjugate in a buffer. Step 1 is carried out by (a) contacting the analyte with the mixt. of synthetic random sequences of nucleounit libraries such that some nucleounits bind the analyte, (b) removing the unbound nucleounits by partitioning, and (c) amplifying the remaining nucleounits by PCR to obtain an enriched soln. of nucleounits with high affinity for the analyte. Thus, a method and lateral flow test strip for detection of cytomegalovirus (CMV) presence in a biol. sample such as serum or urine is described. The strip is prepd. with three solns., one contg. anti-CMV antibodies, one contg. "nucleounit to CMV antibody conjugated to red microparticles" and "red microparticles", and another contg. "nucleounit to colored particles". The "nucleounit" may be an oligonucleotide aptamer specific for anti-CMV antibodies.

L1 ANSWER 51 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:913848 CAPLUS

DOCUMENT NUMBER: 139:206726
TITLE: Molecular basis for anti-**amyloid** therapy in the prevention and treatment of Alzheimer's disease
AUTHOR(S): Gandy, Sam
CORPORATE SOURCE: Farber Institute for Neurosciences, Thomas Jefferson University, Philadelphia, PA, 19107, USA
SOURCE: Neurobiology of Aging (2002), 23(6), 1009-1016
CODEN: NEAGDO; ISSN: 0197-4580
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Amyloid** is a generic description applied to a heterogeneous class of tissue protein ppts. that have the common feature of .beta.-pleated sheet secondary structure, a characteristic that confers affinity of the protein deposit for the histochem. dye Congo red. **Amyloids** may be deposited in a general manner throughout the body (systemic **amyloids**) or confined to a particular organ (e.g., cerebral **amyloid**, renal **amyloid**). Alzheimer's disease (AD) is characterized by clin. evidence of cognitive failure in assocn. with cerebral amyloidosis, as well as cerebral intra-neuronal neurofibrillary pathol., neuronal and synaptic loss, and neurotransmitter deficits. The cerebral **amyloid** of AD is deposited around meningeal and cerebral vessels, as well as in gray matter. In gray matter, the deposits are multi-focal, coalescing into miliary structures known as plaques. Parenchymal **amyloid** plaques are distributed in brain in a characteristic fashion, differentially affecting the cerebrum and hippocampus, while largely sparing the basal ganglia, thalamus, spinal cord, and hindbrain. The main constituent of cerebrovascular **amyloid** is a 40-42-amino acid polypeptide, designated .beta. protein by some and A4 by others, which has entered standardized nomenclature as A.beta. or A-beta. A.beta. is derived from a 695-770 amino acid precursor, termed the **amyloid** precursor protein (APP). The processing of APP and therapeutic manipulation of A.beta. metab. for treatment of AD are discussed.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 52 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:888911 CAPLUS
DOCUMENT NUMBER: 137:368602
TITLE: Antigen-dependent immunosuppression induced by genetic manipulation of B cells using a wide array of genes involved in B cell homeostasis
INVENTOR(S): Sheriff, Ahmed; Vogt, Birgit
PATENT ASSIGNEE(S): Genethor G.m.b.H., Germany
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002092792 | A2 | 20021121 | WO 2002-EP5410 | 20020516 |
| WO 2002092792 | A3 | 20030320 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,

TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: DE 2001-10123764 A 20010516
AB The invention concs. on immunosuppression. According to the invention, the co-stimulation of B-cells is manipulated by introducing a wide array of genes into B cells and using these B cells in controlling physiol. immune response and immunopathol. Gene therapy and immunotherapy using modified B cells in cancers, transplantation, autoimmunity and a variety of other diseases is described.

L1 ANSWER 53 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:856289 CAPLUS
DOCUMENT NUMBER: 138:313698
TITLE: Therapeutic approaches to the treatment of Alzheimer's disease
AUTHOR(S): Yamada, Kiyofumi; Toshitaka, Nabeshima
CORPORATE SOURCE: Laboratory of Experimental Therapeutics, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa, Japan
SOURCE: Drugs of Today (2002), 38(9), 631-637
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Alzheimer's disease is the most common cause of progressive decline of cognitive function in aged humans and is characterized by the presence of numerous senile plaques and neurofibrillary tangles accompanied by neuronal loss. The only treatment currently available for the disease is pharmacotherapy with acetylcholinesterase inhibitors, a palliative strategy aimed at the temporary improvement of cognitive function. Other strategies with disease-modifying potential may include the use of antiinflammatory drugs, **estrogen** replacement therapy and antioxidants. Recent progress in understanding the mol. and cellular pathophysiol. of Alzheimer's disease has suggested possible pharmacol. interventions that could modify the development and progress of the disease (disease-modifying therapy), such as treatment with secretase inhibitors, transition metal chelators, HMG-CoA reductase inhibitors and **amyloid**-.beta. immunization. Inhibitors of tau hyperphosphorylation may also modulate the development and progress of the disease.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 54 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:754564 CAPLUS
DOCUMENT NUMBER: 137:261880
TITLE: Antigen-dependent reduction of specific immune reactions by influencing the co-stimulation for treatment of autoimmune disease, allergy, transplantation
INVENTOR(S): Sheriff, Ahmed
PATENT ASSIGNEE(S): Genethor G.m.b.H., Germany
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| WO 2002077208 | A1 | 20021003 | WO 2002-EP3292 | 20020323 | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2001-107578 A 20010327

AB The invention relates to a redn. in specific immune reactions. According to the method, antigen-presenting cells are stimulated to present defined antigens with simultaneous prodn. of a PD-1 binding mol. The PD-1 binding mol. is preferably PD-L1, PD-L2, an antibody, or a monoclonal antibody. The antigen-presenting cells have been transfected to present only one defined antigen, which can be an autoantigen, allergen, or anything that causes an unwanted immune response. The antigen-presenting cells also display a high no. of homing receptor CD44, and if necessary a CTLA-4 binding mol., and if necessary mols. which suppress B7 and/or CD40. The antigen-presenting cells can be used in treatment of autoimmune disease, allergy and transplantation.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 55 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:710463 CAPLUS

DOCUMENT NUMBER: 138:280555

TITLE: Development of anti-dementia drugs for Alzheimer's disease: present and future

AUTHOR(S): Nabeshima, Toshitaka; Yamada, Kiyofumi

CORPORATE SOURCE: Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya, 466-8560, Japan

SOURCE: Advances in Behavioral Biology (2002), 51(Mapping the Progress of Alzheimer's and Parkinson's Disease), 223-228
CODEN: ADBBBW; ISSN: 0099-6246

PUBLISHER: Plenum Publishing Corp.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Alzheimer's disease (AD) is a neurodegenerative disorder that is neuropathol. characterized by the presence of numerous senile plaques and neurofibrillary tangles accompanied by neuronal loss. The extracellular senile plaques are composed of **amyloid** .beta.-peptides (A.beta.), 40-42-amino acid peptide fragments of the .beta.-**amyloid** precursor protein (APP), whereas the intracellular neurofibrillary tangles are composed of highly phosphorylated tau proteins. Clin. manifestations of AD are primarily the progressive loss of memory and language. With disease progression, patients may have psychiatric and behavioral disturbances. In this article, we reviewed the recent progress in pharmacotherapy for AD, as well as possible future therapeutic strategies.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 56 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:694993 CAPLUS

DOCUMENT NUMBER: 137:350697

TITLE: Ovariectomy of young mutant **amyloid**

precursor protein transgenic mice leads to increased mortality
AUTHOR(S): Levin-Allerhand, Justine A.; Smith, Jonathan D.
CORPORATE SOURCE: The Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of Molecular Neuroscience (2002), 19(1/2), 163-166
CODEN: JMNEES; ISSN: 0895-8696
PUBLISHER: Humana Press Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alzheimer disease (AD) is a neurodegenerative disease affecting a large percentage of the elderly population. Preventative therapies for AD have been limited; however, epidemiol. studies have demonstrated that **estrogen** replacement therapy may prevent or delay the onset of AD. Therefore, we utilized female mutant **amyloid** precursor protein transgenic mice (APPSWE), as a mouse model of AD-like pathol., to study the long-term effects of **estrogen** withdrawal. Interestingly, by 8 mo of age 58% of the ovariectomized APPSWE mice had died, whereas there was no mortality in the sham ovariectomized APPSWE mice. This mortality was correlated with **estrogen** loss only in the APPSWE mice since background strain matched ovariectomized wild-type mice had virtually no mortality. Cerebral A.beta. levels in the surviving APPSWE ovariectomized females were increased by 50% compared to the sham ovariectomized APPSWE females. However, the levels of A.beta. in the ovariectomized APPSWE mice were still well below those obsd. in 2-yr-old APPSWE mice that had A.beta. plaques. Therefore, the mildly increased A.beta. levels were not the suspected cause of death in these ovariectomized mice. Previous studies have demonstrated increased mortality in mice overexpressing mutant or wildtype APP independent of A.beta. accumulation; thus, **estrogen** withdrawal may potentiate this phenotype assocd. with APP overexpression.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 57 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:658272 CAPLUS
DOCUMENT NUMBER: 137:196686
TITLE: A split ubiquitin fusion protein as a reporter for the detection of conformational changes in proteins
INVENTOR(S): Johnsson, Nils; Raquet, Xavier; Varshavsky, Alexander J.; Eckert, Jorg H.
PATENT ASSIGNEE(S): Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V., Germany
SOURCE: PCT Int. Appl., 176 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002066656 | A2 | 20020829 | WO 2002-US325 | 20020103 |
| WO 2002066656 | A3 | 20030227 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1349943 A2 20031008 EP 2002-718797 20020103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2001-259827P P 20010104
WO 2002-US325 W 20020103

AB The invention provides methods and reagents for monitoring protein structure by an intrapolypeptide split-ubiquitin assay. A method of using a reporter protein flanked by N- and C-terminal domains of ubiquitin to monitor conformational changes in proteins is described. The central domain of the fusion protein includes a domain that undergoes a specific, conformation-dependent interaction with a protein of interest. If the ubiquitin fusion protein can interact with the target, the protein is protected against ubiquitin-dependent degrdn. If the interaction is blocked, the ubiquitin domains can dimerize, leading to degrdn. of the fusion protein and loss of a reporter signal. The method can be used to study the effects of external stimuli or mutation on protein conformation.

L1 ANSWER 58 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:643755 CAPLUS
DOCUMENT NUMBER: 138:197987
TITLE: Antioxidant neuroprotection in Alzheimer's disease as preventive and therapeutic approach
AUTHOR(S): Behl, Christian; Moosmann, Bernd
CORPORATE SOURCE: Max Planck Institute of Psychiatry, Munich, Germany
SOURCE: Free Radical Biology & Medicine (2002), 33(2), 182-191
CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Various neurodegenerative disorders and syndromes are assocd. with oxidative stress. The deleterious consequences of excessive oxidns. and the pathophysiol. role of reactive oxygen species (ROS) have been intensively studied in Alzheimer's disease (AD). Neuronal cell dysfunction and oxidative cell death caused by the AD-assocd. **amyloid** .beta. protein may causally contribute to the pathogenesis of AD. Antioxidants that prevent the detrimental consequences of ROS are consequently considered to be a promising approach to neuroprotection. While there is ample exptl. evidence demonstrating neuroprotective activities of antioxidants in vitro, the clin. evidence that antioxidant compds. act as protective drugs is still relatively scarce. Nevertheless, antioxidants constitute a major part of the panel of clin. and exptl. drugs that are currently considered for AD prevention and therapy. Here, focus is put mainly on phenolic antioxidant structures that belong to the class of direct antioxidants. Exptl. and clin. evidence for the neuroprotective potential of .alpha.-tocopherol (vitamin E) and 17.beta.-estradiol (**estrogen**) is shortly summarized and an outlook is given on possible novel antioxidant lead structures with improved pharmacol. features.

REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 59 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:640201 CAPLUS
DOCUMENT NUMBER: 137:346468
TITLE: Cellular and molecular targets of **estrogen** in normal human breast tissue
AUTHOR(S): Seth, Pankaj; Porter, Dale; Lahti-Domenici, Jaana; Geng, Yan; Richardson, Andrea; Polyak, Kornelia
CORPORATE SOURCE: Department of Adult Oncology, Dana-Farber Cancer Institute and Department of Medicine, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Cancer Research (2002), 62(16), 4540-4544

CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To gain insight into the in vivo role of **estrogen**, we isolated **estrogen** receptor-pos. cells from normal human breast tissue using a recombinant adenovirus that expresses green fluorescence protein in response to **estrogen**. We compared the global gene expression profile of these **estrogen** receptor-pos. cells with that of various normal and cancerous mammary epithelial cells and identified several genes not implicated previously in **estrogen** signaling. One of these genes, lipocalin 2, is a putative in vivo **estrogen** target gene and paracrine factor that mediates the growth regulatory effects of **estrogen** in normal breast epithelium. These results demonstrate that normal and cancerous **estrogen** receptor-pos. cells are distinct at the mol. level and suggest that lipocalin 2 is a new therapeutic target for breast cancer prevention and treatment.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 60 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:633469 CAPLUS
DOCUMENT NUMBER: 137:274252
TITLE: The effects of .beta.-estradiol on SH-SY5Y neuroblastoma cells during heavy metal induced oxidative stress, neurotoxicity and .beta.-**amyloid** secretion
AUTHOR(S): Olivieri, G.; Novakovic, M.; Savaskan, E.; Meier, F.; Baysang, G.; Brockhaus, M.; Muller-Spahn, F.
CORPORATE SOURCE: Neurobiology Laboratory, Psychiatric University Hospital, Basel, CH-4025, Switz.
SOURCE: Neuroscience (Oxford, United Kingdom) (2002), 113(4), 849-855
CODEN: NRSCDN; ISSN: 0306-4522
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The role of **estrogen** as a neurotrophic/neuroprotective agent in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases is increasingly being shown. In this study, the authors examd. the neuroprotective effects of .beta.-estradiol on SH-SY5Y neuroblastoma cells which have been exposed to the heavy metals cobalt and mercury. The results show that cobalt and mercury are able to induce oxidative stress and cell cytotoxicity and increase the secretion of .beta.-**amyloid** 1-40 and 1-42. These deleterious effects are reversed by pretreatment of the cells with .beta.-estradiol. It is further shown that .beta.-estradiol exerts its neuroprotective action through mechanisms which reduce oxidative stress and reduce .beta.-**amyloid** secretion. Pretreatment of the cells with .alpha.-estradiol did not alleviate the toxic effects of the heavy metals. The results are significant as they contribute to a better understanding of the mode of action of **estrogen** with relevance to its use in the treatment of neurodegenerative disorders.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 61 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:623034 CAPLUS
DOCUMENT NUMBER: 137:333287
TITLE: **Estrogen**-mediated neuroprotection against .beta.-**amyloid** toxicity requires expression of **estrogen** receptor .alpha. or .beta. and

activation of the MAPK pathway
AUTHOR(S): Fitzpatrick, Jennifer L.; Mize, Amy L.; Wade, Christian B.; Harris, Julie A.; Shapiro, Robert A.; Dorsa, Daniel M.
CORPORATE SOURCE: Department of Pharmacology, University of Washington, Seattle, WA, USA
SOURCE: Journal of Neurochemistry (2002), 82(3), 674-682
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It is well documented that **estrogen** can activate rapid signaling pathways in a variety of cell types. These non-classical effects of **estrogen** have been reported to be important for cell survival after exposure to a variety of neurotoxic insults. Since direct evidence of the ability of the **estrogen** receptors (ERs) .alpha. and/or .beta. to mediate such responses is lacking, the hippocampal-derived cell line HT22 was stably transfected with either ER.alpha. (HTER.alpha.) or ER.beta. (HTER.beta.). In HTER.alpha. and HTER.beta. cells, but not untransfected cells, an increase in ERK2 phosphorylation was measured within 15 min of 17.beta.-estradiol treatment. The ER antagonist ICI 182780 (1 .mu.M) and the MEK inhibitor, PD 98059 (50 .mu.M) blocked this increase in ERK2 phosphorylation. Treatment of HT22, HTER.alpha. and HTER.beta. cells with the .beta.-**amyloid** peptide (25-35) (10 .mu.M) resulted in a significant decrease in cell viability. Pretreatment for 15 min with 10 nM 17.beta.-estradiol resulted in a 50% increase in the no. of living cells in HTER.alpha. and HTER.beta. cells, but not in HT22 cells. Finally, ICI 182 780 and PD 98059 prevented 17.beta.-estradiol-mediated protection. This study demonstrates that both ER.alpha. and ER.beta. can couple to rapid signaling events that mediate **estrogen**-elicited neuroprotection.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 62 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:607477 CAPLUS
DOCUMENT NUMBER: 138:87485
TITLE: Identification of mRNAs differentially-expressed between benign and malignant breast tumour cells
AUTHOR(S): Liu, D.; Rudland, P. S.; Sibson, D. R.; Barraclough, R.
CORPORATE SOURCE: School of Biological Sciences, University of Liverpool, Liverpool, L69 7ZB, UK
SOURCE: British Journal of Cancer (2002), 87(4), 423-431
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two suppression subtracted cDNA libraries have been constructed, one contg. cDNAs to mRNAs present at a higher level in a benign human breast tumor-derived cell line relative to the malignant mammary cell line, MCF-7, and the other contg. cDNAs present at a higher level in the MCF-7 cells relative to the benign cells. Randomly-picked cloned DNAs have been sequenced yielding 29 and 128 different cDNAs from the benign and malignant libraries, resp. Using reverse Northern hybridization, 76% and 83% of the cDNAs were differentially expressed by greater than two-fold, while 14% and 11% of cDNAs in the resp. libraries were differentially expressed by more than 15-fold. Amongst these were **estrogen** -responsive cDNAs and expressed sequence tags. One such **estrogen** -responsive expressed sequence tag, M41, is transcribed from a gene located on chromosome 21q22.3, within an intron of a larger gene. The M41 gene contains **estrogen** response elements, one of which is

assocd. with alu repeats. M41 mRNA is expressed at a statistically significantly higher level in human breast cancer specimens than in normal human breast and benign lesions. In carcinomas, its up-regulation is assocd. with the development of the malignant cell.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 63 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:521682 CAPLUS
DOCUMENT NUMBER: 137:242286
TITLE: **Estrogen** can prevent or reverse obesity and diabetes in mice expressing human islet **amyloid** polypeptide
AUTHOR(S): Geisler, John G.; Zawalich, Walter; Zawalich, Kathleen; Lakey, Jonathan R. T.; Stukenbrok, Hans; Milici, Anthony J.; Soeller, Walter C.
CORPORATE SOURCE: Yale University, New Haven, CT, USA
SOURCE: Diabetes (2002), 51(7), 2158-2169
CODEN: DIAEAZ; ISSN: 0012-1797
PUBLISHER: American Diabetes Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Type 2 diabetes is characterized by loss of .beta.-cell mass and concomitant deposition of **amyloid** derived from islet **amyloid** polypeptide (IAPP). Previously the authors have shown that expression of human IAPP (huIAPP) in islets of transgenic mice results in either a rapid onset of hyperglycemia in mice homozygous for the huIAPP transgene on a lean background (FVB/N) or a gradual hyperglycemia in mice hemizygous for the huIAPP transgene on an obese background (Avy/A). In both strains, only the males routinely develop diabetes. To investigate this sexual dimorphism, the authors treated young prediabetic Avy/A mice transgenic for huIAPP (huIAPP-Avy) with 17.beta.-estradiol (E2). The treatment completely blocked the progression to hyperglycemia but also prevented the assocd. wt. gain in these mice. Immunohistochem. of pancreatic sections demonstrated normal islet morphol. with no apparent deposition of islet **amyloid**. E2 treatment of 1-yr-old huIAPP-Avy diabetic males rapidly reverses obesity and hyperglycemia. To det. the effects of E2 in a nonobese model, the authors also treated prediabetic, ad libitum-fed and pair-fed Lean-huIAPP transgenic males. E2 completely blocked the progression to hyperglycemia with no significant effect on body wt. Pancreatic insulin content and plasma insulin concn. of Lean-huIAPP transgenic mice increased in a dose-dependent manner. The authors demonstrated the presence of **estrogen** receptor (ER)-.alpha. mRNA in mouse and human islets. By also confirming the presence of ER-.alpha. protein in islets, the authors discovered a novel 58-kDa ER-.alpha. isoform in mice and a 52-kDa isoform in humans, in the absence of the classic 67-kDa protein found in most tissues of both species. The demonstrated presence of ER-.alpha. in mouse and human islets is consistent with a direct effect on islet function. The authors conclude that exogenous E2 administered to male mice may block human IAPP-mediated .beta.-cell loss both by direct action on .beta.-cells and by decreasing insulin demand through inhibition of wt. gain or increasing insulin action.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 64 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:521369 CAPLUS
DOCUMENT NUMBER: 137:226772
TITLE: Neuroprotective and neurotrophic efficacy of phytoestrogens in cultured hippocampal neurons
AUTHOR(S): Zhao, Lixia; Chen, Qi; Brinton, Roberta Diaz

CORPORATE SOURCE: Department of Molecular Pharmacology and Toxicology and Neuroscience Program, Pharmaceutical Sciences Center, University of Southern California, Los Angeles, CA, 90089, USA

SOURCE: Experimental Biology and Medicine (Maywood, NJ, United States) (2002), 227(7), 509-519
CODEN: EBMMBE; ISSN: 1535-3702
PUBLISHER: Society for Experimental Biology and Medicine
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epidemiol. data from retrospective and case-control studies have indicated that **estrogen** replacement therapy (ERT) can decrease the risk of developing Alzheimer's disease. In addn., ERT has been found to promote cellular correlates of memory and to promote neuronal survival both in vivo and in vitro. Phytoestrogens have been proposed as potential alternatives to ERT. To det. whether phytoestrogens exert **estrogen** agonist effect in neural tissue, investigations of neuroprotective and neurotrophic efficacy of phytoestrogens were conducted. Six phytoestrogens, genistein, genistin, daidzein, daidzin, formononetin, and equol, were tested for their neuroprotective efficacy against two toxic insults, glutamate excitotoxicity and .beta.-amyloid25-35. Neuronal membrane damage was quant. measured by lactate dehydrogenase (LDH) release, and neuronal mitochondrial viability was detd. by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay. Results of these studies demonstrated that all phytoestrogens induced a modest but significant redn. in LDH release following exposure to glutamate and .beta.-amyloid25-35. In contrast, none of phytoestrogens induced a significant increase in reduced MTT levels, which occurred in the presence of a full **estrogen** agonist, 17.beta.-estradiol. Anal. of the neurotrophic potential of genistein and daidzein, two phytoestrogens that exerted a significant redn. in LDH release, demonstrated that neither of these mols. promoted hippocampal neuron process outgrowth. Of these analyses indicate that although phytoestrogens exert a neuroprotective effect at the plasma membrane, they do not sustain neuron mitochondrial viability nor do they induce cellular correlates of memory as neurite outgrowth and synaptogenesis are putative mechanisms of memory. Data derived from these investigations would predict that phytoestrogens could exert some neuroprotective effects analogous to that of antioxidants, but that these mols. are not functional equiv. to endogenously active 17.beta.-estradiol or to **estrogen** replacement formulations and, therefore, would raise the concern that they may not reduce the risk of Alzheimer's disease or sustain memory function in post-menopausal women.

REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 65 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:520659 CAPLUS
DOCUMENT NUMBER: 137:200716

TITLE: Effects of high- and low-isoflavone (phytoestrogen) soy foods on inflammatory biomarkers and proinflammatory cytokines in middle-aged men and women

AUTHOR(S): Jenkins, David J. A.; Kendall, Cyril W. C.; Connelly, Philip W.; Jackson, Chung-Ja C.; Parker, Tina; Faulkner, Dorothea; Vidgen, Edward

CORPORATE SOURCE: Clinical Nutrition and Risk Factor Modification Center, Division of Endocrinology and Metabolism, St Michael's Hospital, Toronto, ON, M5C 2T2, Can.

SOURCE: Metabolism, Clinical and Experimental (2002), 51(7), 919-924
CODEN: METAAJ; ISSN: 0026-0495
PUBLISHER: W. B. Saunders Co.

DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study sought to det. effects of high- and low-isoflavone soy protein foods on acute-phase proteins and proinflammatory cytokines and whether isoflavone phytoestrogens might act as **estrogens**, which enhance the immune response. Forty-one hypercholesterolemic men and postmenopausal women underwent three 1-mo diets consisting of a low-fat dairy food control phase and high- and low-isoflavone soy food test phases (50 g/d and 52g/d soy protein, resp., and 73 mg/d and 10 mg/d isoflavone, resp.). Diets were low in satd. fat (<5% of energy) and cholesterol (<50 mg/d). Fasting blood analytes and blood pressure were measured at the start and end of each phase. For the entire group of subjects, no treatment differences were obsd. for acute-phase proteins or proinflammatory cytokines. However, a significant interaction was noted between diet and sex. Assessing the results of men and women sep., women showed significantly higher interleukin-6 (IL-6) values after the high-isoflavone soy diet (P =.013) compared to control values. For women, the difference between the high- and low-isoflavone IL-6 values was significant using the unadjusted data (P =.048) but not after adjustment. No significant effects were seen for men or women in C-reactive protein (CRP), serum **amyloid** A (SAA), or tumor necrosis factor-.alpha. (TNF-.alpha.). Thus, high levels of isoflavone intake appear to increase serum concns. of IL-6 in women. This finding may indicate an estrogenic effect of soy isoflavones in enhancing the immune response and provide a possible explanation through enhanced immune surveillance for lower incidence of certain cancers in soy-eating parts of the world.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 66 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:488053 CAPLUS
DOCUMENT NUMBER: 137:41769
TITLE: Methods using cholesterol-lowering agents for decreasing .beta. **amyloid** protein
INVENTOR(S): Yankner, Bruce A.; Nadeau, Philip
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 5 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2002081263 | A1 | 20020627 | US 1999-239387 | 19990128 |
| US 6440387 | B2 | 20020827 | | |
| US 2002120003 | A1 | 20020829 | US 2002-86398 | 20020228 |
| US 2002183379 | A1 | 20021205 | US 2002-198331 | 20020714 |
| PRIORITY APPLN. INFO.: | | | US 1998-46235 A3 | 19980323 |
| | | | US 1999-239387 A3 | 19990128 |

AB Blood cholesterol levels are correlated with prodn. of **amyloid** .beta. protein (A.beta.), and are predictors of populations at risk of developing AD. Methods for lowering blood cholesterol levels can be used to decrease prodn. of A.beta., thereby decreasing the risk of developing AD. The same methods and compns. can also be used for treating individuals diagnosed with AD. Methods include administration of compds. which increase uptake of cholesterol by the liver, administration of compds. which block endogenous cholesterol prodn., e.g. administration of HMG-CoA reductase inhibitors, administration of compns. which prevent uptake of dietary cholesterol, and administration of combinations of any of these which are effective to lower blood cholesterol levels. Methods

have also been developed to predict populations at risk, based on the role of cholesterol in prodn. of A.beta.. For example, individuals with ApoE4 and high cholesterol, defined as a blood cholesterol level of greater than 200 mg/dL, post-menopausal women with high cholesterol levels, esp. those who are not taking **estrogen**, or individuals which high blood cholesterol levels who are not obese, are all at risk of developing AD if blood cholesterol levels are not decreased.

L1 ANSWER 67 OF 212 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:442057 CAPLUS
DOCUMENT NUMBER: 137:345414

L33 ANSWER 13 OF 63 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 10
Full-text
AN 2001:794745 CAPLUS
TI Testosterone attenuates β-amyloid toxicity in cultured hippocampal neurons
AU Pike, Christian J.
CS Andrus Gerontology Center, University of Southern California, Los Angeles, CA, 90089-0191, USA
SO Brain Res. (2001), 919(1), 160-165
CODEN: BRREAP; ISSN: 0006-8993
PB Elsevier Science B.V.
DT Journal
LA English
AB Accumulating evidence suggests that **testosterone** has neurotrophic and perhaps neuroprotective actions. Thus, age-related depletion of **testosterone** may increase the brain's vulnerability to **Alzheimer**'s disease and related disorders. To begin investigating this issue, cultured neurons were exposed to the **Alzheimer**-related insult β-amyloid in the presence of **testosterone**. β-Amyloid neurotoxicity was significantly reduced by **testosterone** via a rapid, estrogen-independent mechanism. These data may provide addnl. insight into the treatment of age-related neurodegenerative disorders.

L47 ANSWER 6 OF 18 Elsevier BIOBASE COPYRIGHT 2001 Elsevier Science B.V.
DUPLICATE
AN 1999156433 ESBIOBASE
TI Benzolactam (BL) enhances sAPP secretion in fibroblasts and in PC12 cells
AU Ibarreta D.; Duchen M.; Ma D.; Qiao L.; Kozikowski A.P.; Etcheberrigaray R.
CS R. Etcheberrigaray, Laboratory of Applied Neuroscience, Cognitive/Computational Sci. Inst., Georgetown University Medical Center, 3970 Reservoir Road NW, Washington, DC 20007, United States.
SO NeuroReport, (06 APR 1999), 10/5 (1035-1040), 33 reference(s)
CODEN: NERPEZ ISSN: 0959-4965
DT Journal; Article
CY United Kingdom
LA English
SL English
AB ACTIVATION of protein kinase C is known to favor the .alpha.-secretase processing of the Alzheimer's disease (AD) **amyloid** precursor protein (APP), resulting in the generation of non-amyloidogenic soluble APP (sAPP). Consequently, the relative secretion of amyloidogenic A.beta..sub.1.sub.-.sub.4.sub.0 and A.beta.(1- 42(3)) is reduced. This is particularly relevant since fibroblasts and other cells expressing APP and **presenilin** AD **mutations** secrete increased amounts of total A.beta. and/or increased **ratios** of A.beta.(1-42(3))/A.beta..sub.1.sub.-.sub.4.sub.0. Interestingly, PKC defects have been found in AD brain (.alpha. and .beta. isoforms) and in fibroblasts (.alpha. isoform) from AD patients. Here, we use a novel PKC activator (benzolactam, BL) with improved selectivity for the .alpha., .beta. and .gamma. isoforms to enhance sAPP secretion in fibroblasts from AD patients and in PC12 cells. Incubation (2 h) of AD fibroblasts with BL (1 and 10 .mu.M) resulted in significant increases of sAPP secretion over basal levels. sAPP secretion in BL-treated AD cells was also slightly higher compared to control BL-treated fibroblasts, which only showed significant increases of sAPP secretion after treatment with 10 .alpha.M BL. Staurosporine (a PKC inhibitor) eliminated the effects of BL in both control and AD fibroblasts. BL and a related compound (LQ12) also caused an .sim.3-fold sAPP secretion in PC12 cells. The use of a novel and possibly non-tumorigenic PKC activator may prove useful to favor non-amyloidogenic APP processing and is, therefore, of potential therapeutic value.

L47 ANSWER 7 OF 18 Elsevier BIOBASE COPYRIGHT 2001 Elsevier Science B.V.
DUPLICATE
AN 1999104285 ESBIOBASE
TI Enhancement of **amyloid** .beta. 42 secretion by 28 different **presenilin** 1 **mutations** of familial Alzheimer's disease
AU Murayama O.; Tomita T.; Nihonmatsu N.; Murayama M.; Sun X.; Honda T.; Iwatsubo T.; Takashima A.
CS A. Takashima, Laboratory for Alzheimer's Disease, Brain Science Institute, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan.
SO Neuroscience Letters, (09 APR 1999), 265/1 (61-63), 14 reference(s)
CODEN: NELED5 ISSN: 0304-3940
PUI S0304394099001871
DT Journal; Article
CY Ireland
LA English
SL English
AB Families bearing **mutations** in the **presenilin** 1 (PS1) gene develop early onset familial Alzheimer's disease (FAD). Further, some PS1 mutants enhance secretion of the longer form of **amyloid** .beta. protein (A.beta.42). We constructed cDNAs encoding human PS1 harboring 28 FAD-linked mutations, and examined the effects of the expressed PS1 mutants on A.beta.42 secretion in .beta. **amyloid** precursor producing COS-1 cells. All the mutants significantly enhanced the **ratio** of A.beta.42 to total A.beta. compared with wild-type PS1. However, the increase in A.beta.42 **ratio** in cells with each PS1 mutation did not correlate with the reported age of onset of FAD caused by that mutation. These results suggest that increased A.beta.42 secretion is important for the development of Alzheimer's disease (AD), but may not be the only factor contributing to the onset of AD.

L33 ANSWER 16 OF 63 PROMT COPYRIGHT 2001 Gale Group
Full-text

AN 2000:550990 PROMT
TI **Alzheimer**'s disease may be inhibited by **testosterone**.
SO Urology Times, (May 2000) Vol. 28, No. 5, pp. 34.
ISSN: 0093-9722.
PB Advanstar Communications, Inc.
DT Newsletter
LA English
WC 129
*FULL TEXT IS AVAILABLE IN THE ALL FORMAT*
AB Researchers at Rockefeller University in New York believe that **testosterone** supplements may eventually help prevent **Alzheimer**'s disease. Their study, published in the Proceedings of the National Academy of Sciences (2000; 97:1202-5), found that extra **testosterone** added to nerve cells inhibited the process of plaque formation in the brain.

| L Number | Hits | Search Text | DB | Time stamp |
|---|---|---|---|---|
| - | 252 | amyloid and estrogen | USPAT; EPO; JPO; DERWENT | 2004/01/29 16:50 |
| - | 0 | amyloid and equine adj estrogen | USPAT; EPO; JPO; DERWENT | 2004/01/29 16:49 |
| - | 112 | equine adj estrogen | USPAT; EPO; JPO; DERWENT | 2004/01/29 16:49 |
| - | 0 | (amyloid and estrogen) and alzhaimer | USPAT; EPO; JPO; DERWENT | 2004/01/29 16:49 |
| - | 11 | (amyloid and estradiol) and equine | USPAT; EPO; JPO; DERWENT | 2004/01/29 16:55 |
| - | 1 | morris and notelivitz | USPAT; EPO; JPO; DERWENT | 2004/01/29 16:55 |
| - | 41 | (amyloid and estrogen) and equine | USPAT; EPO; JPO; DERWENT | 2004/01/29 17:02 |
| - | 21 | "5952374" | USPAT; EPO; JPO; DERWENT | 2004/01/29 17:02 |
| - | 95 | amyloid and estradiol | USPAT; EPO; JPO; DERWENT | 2004/01/29 17:07 |

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| NEWS 8 | OCT 28 | BIOSIS file segment of TOXCENTER reloaded and enhanced |
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| NEWS 10 | DEC 08 | CABA reloaded with left truncation |
| NEWS 11 | DEC 08 | IMS file names changed |
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| NEWS 13 | DEC 09 | STN Entry Date available for display in REGISTRY and CA/CAplus |
| NEWS 14 | DEC 17 | DGENE: Two new display fields added |
| NEWS 15 | DEC 18 | BIOTECHNO no longer updated |
| NEWS 16 | DEC 19 | CROPU no longer updated; subscriber discount no longer available |
| NEWS 17 | DEC 22 | Additional INPI reactions and pre-1907 documents added to CAS databases |
| NEWS 18 | DEC 22 | IFIPAT/IFIUDB/IFICDB reloaded with new data and search fields |
| NEWS 19 | DEC 22 | ABI-INFORM now available on STN |
| NEWS 20 | JAN 27 | Source of Registration (SR) information in REGISTRY updated and searchable |
| NEWS 21 | JAN 27 | A new search aid, the Company Name Thesaurus, available in CA/CAplus |

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| NEWS LOGIN | Welcome Banner and News Items |
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